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Embryoprotective Therapy of Infertile Women with Polycystic Ovary Syndrome

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1. Introduction

1.1 Definition of infertility and habitual abortion

Infertility is defined as an inability of a woman to carry a pregnancy to a viable foetus. From the perspective of differential diagnosis, infertility differs from sterility, i.e. an inability of a woman to get pregnant. If a woman miscarries on at least three consecutive occasions, this is termed habitual abortion (or habitual pregnancy loss, HPL). Habitual abortion is a stand-alone nosological unit rather than an accumulation of circumstantial factors, as is confirmed by the lower incidence of foetal chromosomal aberrations in repeatedly miscarrying women compared to spontaneous abortions and a greater involvement of peristatic factors. A loss of all consecutive pregnancies in the first or second trimester is termed primary recurrent miscarriage. Secondary recurrent miscarriage is a situation when repeated miscarriages are preceded by a pregnancy leading to childbirth or an induced abortion. The term dysfertility is used if a woman miscarries on two consecutive occasions only (Zwinger, 2004).

1.2 Epidemiology and etiology of habitual abortion

Habitual abortion occurs in 1% of women in reproductive age and 15–38% of pregnancies result in spontaneous abortion. This number is, nevertheless, likely to be much higher as more than 40% of conceptions end before pregnancy is diagnosed (Madar, 2002). The frequency of spontaneous abortions increases with mother's age. Up to 90% of the first spontaneous abortions result from, usually de novo, chromosomal aneuploidy, whereas the risk of recurrence of the same abnormality is minimal (Roztočil, 2001). Causes of habitual abortion include age, anatomy factors, genetic factors, haematology factors, endocrine factors, infections, immunology factors, environmental factors, psychological factors, idiopathic factors.

1.3 Prerequisites of successful treatment of habitual abortion

Successful therapy of infertile women is subject to a careful and individualised differential diagnosis of habitual abortions. Comprehensive evaluation aimed at identification of the specific cause of infertility should be performed in the pregnant women who have previously repeatedly lost their pregnancy. Rigorous approach to diagnose the causes of repeated miscarriage is essential when an effective therapy is to be selected. Causal therapy

of habitual pregnancy loss includes conservative pharmacological treatment, surgery and lifestyle changes.

2. Endocrine causes of recurrent pregnancy losses

An endocrinopathy is a common and severe cause of infertility. These are either gynaecology-related endocrinopathies and gynaecology-unrelated endocrinopathies. Gynaecology-related endocrinopathies results from ovarian hypofunction. Abnormal follicle stimulating/luteinizing hormone (FSH/LH) ratio and hyperandrogenism in the polycystic ovary syndrome are also considered as factors associated with an increased risk of habitual abortions. The proportion of first trimester miscarriages in women with the polycystic ovary syndrome is about 30–50% higher than in healthy women (Kauffman, 2003)

Gynaecology-unrelated endocrinopathies with unequivocal impact on fertility include thyreotoxicosis, hypothyreosis, diabetes mellitus, hyperprolactinaemia and obesity (Krajčovičová, 2007).

2.1 Gynaecology-related endocrinopathies

Epidemiologically, polycystic ovary syndrome is a highly prevalent gynaecology-related endocrinopathy. However, it is not solely a gynaecological condition but rather a disease with a range of metabolic and endocrine findings, including diabetes (Moller, 1993, Toscano, 1998). Ovarian hypofunction as a cause of habitual miscarriages represents another separate nosological unit of endocrinopathies with an impact on female reproductive function.

2.1.1 Polycystic ovary syndrome

It is estimated that polycystic ovary syndrome affects 5 – 10% of women of childbearing potential, with 35 – 45% of polycystic ovary syndrome patients being obese (Svačina, 2001). The real incidence of this syndrome in the population depends on the diagnostic criteria used and is probably higher than that published in the literature. Complications of pregnancy associated with maternal PCOS include increased prevalence of early pregnancy loss (EPL), gestational diabetes (GDM), pregnancy-induced hypertensive disorders (PET/PIH), and the birth of small-for-gestational-age (SGA) babies. Increased risk of EPL has been attributed to obesity, hyperinsulinaemia, elevated luteinizing hormone concentrations, and endometrial dysfunction. Avoiding obesity before pregnancy and treatment with metformin are therapeutic options, also for the increased prevalence of GDM (Homburg, 2006). Administration of metformin throughout pregnancy is a contentious issue. Screening pregnant women with PCOS for GDM and PET/PIH-especially if they are obese-is recommended, although data for a firm association between PCOS and PET/PIH is weak. Impaired insulin-mediated growth and foetal programming are possible explanations for a higher prevalence of SGA infants in mothers with PCOS (Homburg, 2006).

2.1.1.1 Polycystic ovary syndrome - pathophysiology

The mechanism behind metabolic and hormonal disposition for polycystic ovary syndrome, or what the primary disorder is, is rather unclear. Over the recent years, large groups of researchers have been involved in polycystic ovary syndrome research but the results are often controversial and confusing. Insulin resistance and the status of insulin receptors have

frequently been investigated. Page: 3 Higher insulin independent autophosphorylation of insulin receptor at serine residue was observed. The role of IRS substrate disorders is also discussed as is the role of TNF-a, e.g. IRS-1 phosphorylation induced by TNF-a (Svačina, 2001). Defects of the glycoprotein PC-1 are being considered as another potential factor. Insulin resistance in male relatives has recently been shown. Phosphorylation of serine is a process that explains hyperanadrogenism as well as insulin resistance. This is a key process of androgen secretion in an ovary and adrenal glands and there also is important serine phosphorylation on insulin receptors (Svačina, 2001).

A number of studies focused on the clear association with abdominal obesity (even though some of the patients are not particularly obese) and it seems that it is only the women with higher abdominal fat that are insulin resistant and hyperandrogenemic. SHBG reduction is typical, particularly in obese patients. Sex hormone-binding globulin (SHBG) is the primary plasma transport protein for sex steroid hormones and regulates the bioavailability of these hormones to target tissues. The gene encoding SHBG is complex and any of several polymorphisms in SHBG have been associated with alterations in circulating SHBG levels (Chen, 2010). Epidemiological studies have revealed that low plasma SHBG levels are an early indicator of insulin resistance and predict the development of type 2 diabetes mellitus (T2DM) in both men and women. Although association between low SHBG levels and risk of diabetes could be explained by the observation that elevations in insulin suppress hepatic SHBG production. Recent studies documenting that the SHBG-altering polymorphisms are associated with risk of T2DM suggest that SHBG may have a more direct physiologic role in glucose homeostasis (Chen, 2010). However, the exact mechanism(s) underlying this association is not known (Chen, 2010). Non-diabetic women with the polycystic ovary syndrome (PCOS), a common endocrine disorder that is associated with insulin resistance, similarly demonstrate lower levels of SHBG. In light of studies investigating polymorphisms in SHBG and T2DM, our group and others have hypothesized that SHBG may represent a candidate gene for PCOS. In this manuscript, we review studies investigating the association between SHBG polymorphisms and PCOS. In summary, multiple studies in women with PCOS confirm that certain genetic polymorphisms are associated with circulating SHBG levels, but they are not consistently associated with PCOS per se. (Chen, 2010)

According to some authors, insulin resistance can be found in women with anovulation cycles only. Women with polycystic ovary syndrome have lower basal energy expenditure as well as postprandial termogenesis. This is an analogy with android obesity, metabolic syndrome and diabetes. A relative lack of gestagens and, consequently, dominance of cortisol on receptors in abdominal fat may also contribute to the pathogenesis. This results in higher level of free fatty acids and insulin resistance.

To assess the diabetes risk score in polycystic ovary syndrome (PCOS) and in different phenotypes of PCOS and controls was observed and evaluated by overweight premenopausal women with PCOS, non PCOS or controls folowing factors: Finnish Diabetes Risk Score, anthropometrics, oral glucose tolerance test (OGTT), glucose, insulin, and reproductive hormone levels. The women with PCOS had higher adiposity, abdominal adiposity and 120-minute OGTT glucose. The women with PCOS and non-PCOS had elevated 120-minute OGTT insulin compared with controls. The women with PCOS and non-PCOS had similar diabetes risk scores, but both had higher diabetes risk score compared with controls after matching age and BMI. The women with PCOS (4%) and non-PCOS (12%) had a lower prevalence of low risk of diabetes scores compared with controls

(50%) and they have similar Finnish Diabetes Risk Scores and elevated scores relative to controls independent of age and adiposity. Similar clinical screening and treatment practices for type 2 diabetes are warranted for both phenotypes of PCOS (Moran, 2011)

Another research study compared pregnancy outcome, specifically the prevalence of gestational diabetes mellitus (GDM), in a group of patients with polycystic ovary syndrome (PCOS) to a group of healthy weight-matched women. Pregnancies of women with PCOS, who had been treated for infertility were compared with a group of age- and weight-matched controls. There were no significant differences in the prevalence of pregnancy complications such as gestational diabetes mellitus, pregnancy-induced hypertension (PIH) and premature deliveries between the group of PCOS patients and the controls. When differences in age and weight between PCOS patients and controls are negligible, PCOS is not associated with a higher risk of pregnancy complications. (Hašková, 2003)

2.1.1.2 Polycystic ovary syndrome - diagnosis

The international conference in Bethesda in 1990 have recommended three diagnostic criteria: hyperandrogenism, chronic anovulation (enzyme deficits at a level of adrenal glands, e.g. 21-hydroxylase deficit as well as hyperprolactinaemia and androgen-producing tumours should be excluded) and hyperinsulinmia (Svačina, 2001). Frequent, although not exclusive, symptoms include hirsutism, alopecia and acne. There may be no morphological changes on the ovaries. An older definition assumed the presence of at least eight subcapsular cysts in the ovaries of 10 cm in diameter. Higher LH/FSH ratio (usually above 2,0), previous important endocrine diagnostic criterion, is not anymore required for the diagnosis (Toscano, 1998).

2.1.1.3 Polycystic ovary syndrome – treatment

Management of polycystic ovary syndrome (PCOS) usually spans woman's reproductive years. While treatment of androgenic symptoms is often a primary concern, periodically, the regimen has to be modified because of a desire for pregnancy. At this time the couple should be evaluated for factors that may contribute to infertility and this should include semen analysis. However, for many, anovulation is likely to be the cause of infertility and ovulation induction is generally required. The premise on which ovulation induction in PCOS is based is two-fold: increasing ovarian exposure to follicle stimulating hormone (FSH) and/or correcting hormonal derangements. Potential differences in pathogenesis, evidenced clinically by phenotypic diversity, would suggest that treatment should be individualized. These options include the use of clomiphene citrate, insulin sensitizers, and the combination. Protocols for ovulation induction with FSH injections are outlined and the relative risks of multiple gestation and severe ovarian hyperstimulation syndrome. The use of aromatase inhibitors and the occasional use of glucocorticoids are briefly reviewed, and indications for in vitro fertilization and laparoscopic ovarian diathermy outlined (Nader, 2010).

2.1.1.3.1 Clomiphene citrate and insulin sensitizers

The knowledge on the role of insulin resistance in the pathogenesis of PCOS has led to the use of insulin sensitizers in PCOS treatment. Metformin was the first to be used in 1994. Administration of metformin results in decreased androgen and LH levels, improvement in insulin sensitivity and normalization of menstrual cycle (Legro, 2007). Metformin decreases liver gluconeogenesis and reduces oxidation of free fatty acids. It increases uptake of glucose

by skeletal muscles and fat tissue, improves dyslipidemia and it has other specific effects in the ovaries (Mansfield, 2003). Metformin impacts on ovarian steroidogenesis by reducing androgen production, improving the adverse environment of the endometrium and improves ovarian function. It seems so far that metformin (and glitazones) has no or insignificantly positive effect on hirsutism (Šarapatková, 2008). A meta-analysis of metformin studies showed that, compared to placebo, metformin significantly increases the occurrence of ovulation (Lord, 2003). However, it is not clear yet whether treating women with PCOS and with normal BMI and insulin sensitivity with metformin is beneficial. Also, there is a question whether clomiphene should be used alone or in combination with metformin or whether metformin monotherapy should be used to enable infertile women with PCOS to become pregnant and deliver a healthy baby. In a 6-month study comparing all three approaches, clomiphene led to the highest pregnancy and live birth rates. Addition of metformin to therapy in this study did not show a significant advantage over clomiphene monotherapy. However, possible positive effect of this combination cannot be excluded. Induction of ovulation itself does not mean higher likelihood of conceiving and giving birth to a healthy child. Metformin provided, in line with previous findings, an improvement in parameters of insulin sensitivity, BMI, insulin and proinsulin levels, while insulin resistance and testosterone levels declined. Nevertheless, these effects may not be associated with higher rate of live births (Legro, 2007).

Recently, glitazones, other insulin resistance modifying agents, have been tested in women with PCOS. They improve the effects of insulin in the liver, skeletal muscles and fat tissue. Similar to metformin, they also directly impact on ovarian steroidogenesis (Mansfield, 2003). Decrease in insulin levels results in decline in the levels of circulating androgens. Glitazones also reduce the levels of plasminogen activator inhibitor-1. Glitazones are not widely used in clinical practice and they are contraindicated in pregnancy (Šarapatková, 2008). The use of metformin in patients diagnosed with hyperinsulinaemia and in women with the polycystic ovary syndrome represents a therapeutic use of an insulin sensitizer with promising effects in anovulation sterility and dysfertility.

2.1.1.3.2 Protocols for ovulation induction with FSH and in vitro fertilisation

Women with PCOS and a history of habitual abortions or a history of sterility due to anovulation frequently undergo IVF cycles requiring ovarian stimulation with follicle-stimulating hormone (FSH). In his retrospective study, Kdous compared standard long GnRH agonist protocol (Triptolerin) and GnRH antagonist regimens (Cetrorelix) in polycystic ovary syndrome (PCOS) patients undergoing controlled ovarian stimulation (COS) for ICSI cycles. He found that GnRH antagonist protocol is a short and simple protocol with a significant reduction in the incidence of OHSS and gonadotropin levels. However, GnRH antagonist protocol provides a lower live birth rate and an increased risk of early pregnancy loss compared to the GnRH agonist long protocol (Kdous 2009). Well-established micromanipulation techniques, the ICSI and PICSI methods, are successfully used for IVF in women with PCOS. Ovarian hyperstimulation syndrome (OHSS) is a feared complication of IVF. Women with PCOS are at a greater risk of developing OHSS because of the higher number of follicles produced in the ovaries following FSH stimulation (Moosová, 2011).

2.1.1.3.3 Aromatase inhibitors

Aromatase inhibitors block the final step in the enzymatic estrogen production: aromatization of the A-cycle of aromatizable androgens, specifically androstendione and

testosteron. Substances interfering with aromatase activity have been available for many years. However, the substances used during the aminoglutethimide era were non-specific and had a poor safety profile. The third generations of aromatase inhibitors are highly specific and virtually free of adverse events. These substances are licensed for treatment of breast cancer in postmenopausal women with advanced disease or as adjuvant treatment. Temporary inhibition of estradiol production in women with active ovaries leads to increased gonadotropin concentrations and, consequently, stimulation of follicle growth. This is undesirable in patients with ovarian cancer and thus aromatase inhibitors are not used in premenopausal women unless the production of gonadotropins is blocked. On the other hand, this effect is highly desirable in infertile women. Aromatase inhibitors may be used in women who do not ovulate but their no meaning (PCOS-type oligo-ovulation) or in ovulating women in whom higher number of follicles are required (idiopathic infertility, age factor, or prior to IVF). Preliminary studies published thus far show rather convincingly that aromatase inhibitors are effective in inducing ovulation in infertile women (Mitwally, 2006). Letrozole (one of aromatase inhibitors), though reported to be an effective ovulation inducing agent, warrants larger randomized trials. The purpose of this study is to compare the efficacy of letrozole with that of rFSH and clomiphene citrate (CC)/rFSH for ovarian stimulation in IUI cycles. In randomized, prospective, single-blinded clinical trial. 1387 PCOS women after CC failure were randomized into three groups: Group A received letrozole, Group B received CC with two doses rFSH and Group C received continuous rFSH day 2 onwards until hCG injection. RESULTS: Group A, B and C had an ovulation rate of 79.30%, 56.95% and 89.89% and cycle cancellation rate of 20.70%, 43.05% and 10.11%, respectively. Pregnancy rates in Group A, B and C were 23.39%, 14.35% and 17.92%, while the miscarriage rates were 13.80%, 16.67% and 14.52%, respectively. CONCLUSION: Letrozole appears to be a suitable ovulation inducing agent in PCOS women with CC failure and is found to be most effective when baseline estradiol level >60 pg/ml. (Ganesh, 2009).

2.1.1.3.4 Glucocorticoids

In recurrently miscarrying women with PCOS, the presence of high titres of antizonal and antisperm antibodies should be excluded and potential insufficiency of sperm cell head's enzymatic status considered. Patients in whom implantation is a problem, the presence of antizonal and antiendometrial antibodies has to be excluded. High levels of antiphospholipid antibodies and other mechanisms aimed at immunological mother-semi-allogeneic graft tolerance might adversely affect the entire IVF process. Therapy is often carefully selected with respect to a patient's age, character and type of antibodies and the number of IVF cycles. Most frequently, micromanipulation is combined with temporary immunosuppression (short-term administration of glucocorticoids, e.g. Prednison 5mg dosed 1-1/2-0 daily) and long-term antioxidant treatment (Ulčová-Gallová, 2001).

2.1.1.3.5 Treatment by laparoscopic ovarian diathermy

Laparoscopic ovarian drilling is used as one of the options for surgical management of infertility in patients with polycystic ovary syndrome. This method is performed as laparoscopic electrocautery with monopolar needle. Ovarian surface is systematically perforated with a needle and the surgery is frequently combined with a test of tubal patency or hysteroscopy as part of a comprehensive diagnostic laparoscopy. The effect of drilling on

reproductive function was evaluated by a number of studies. Kong compared the effects of laparoscopic ovarian drilling in treating infertile polycystic ovarian syndrome in patients with and without metabolic syndrome. A total of 89 infertile anovulatory polycystic ovarian syndrome patients, who underwent laparoscopic ovarian drilling with completed metabolic screening and seen over a 5-year period. The main outcome measures were clinical, hormonal and metabolic characteristics, as well as spontaneous ovulation rates, reproductive outcomes, and a risk of gestational diabetes after laparoscopic ovarian drilling. Approximately one fifth (21%) of polycystic ovary syndrome patients had metabolic syndrome. There were no differences in spontaneous ovulation rates (68% vs 61%, P=0.76), cumulative pregnancy rates (68% vs 61%, P=0.77), and a risk of gestational diabetes (64% vs 42%, P=0.13) between patients with and without metabolic syndrome. Laparoscopic ovarian drilling was equally effective in inducing ovulation in polycystic ovary syndrome patients with metabolic syndrome. Thus, patients with metabolic syndrome should not be excluded from laparoscopic ovarian drilling, which has an additional advantage of enabling concurrent full tubo-peritoneal assessment (Kong, 2010).

In randomized double-blind placebo-controlled pilot study Nasr evaluated N-acetyl-cysteine (NAC) as an adjunctive therapy following unilateral laparoscopic ovarian drilling (LOD) for clomiphene citrate-resistant women with polycystic ovary syndrome (PCOS). Patients with clomiphene citrate-resistant PCOS who underwent unilateral LOD were assigned randomly to receive either NAC 1.2 g/d or placebo for 5 days starting at day 3 of the cycle for 12 consecutive cycles. The primary outcome was pregnancy rate; secondary outcomes were ovulation rates, endometrial thickness and pregnancy outcome. Baseline clinical, endocrine, and sonographic characteristics were similar in the two groups. A significant increase in both ovulation and pregnancy rates was observed in the NAC group, compared with placebo [87% versus 67% (RR 1.3; 95% CI 1.2-2.7) and 77% versus 57% (RR 1.4; 95% CI 1.1-2.7), respectively, P<0.01]. Moreover, miscarriage rates were significantly lower and live birth rates were significantly higher in the NAC group [8.7% versus 23.5% (RR 0.4; 95% CI 0.1-3.7) and 67% versus 40% (RR 1.7; 95% CI 0.3-3.5), respectively, P<0.01]. NAC, a novel adjuvant therapy to be used following unilateral LOD, might improve overall reproductive outcome (Nasr, 2010).

2.1.2 Ovarian hypofunction

The main therapeutic aim of ovarian hypofunction management is to treat fertility disorders and to substitute the lacking hormones. Treatment of ovarian hypofunction-related dysfertility by assisted reproduction methods represents a complex issue. This group of patients (“low responders”) typically presents with low ovarian response to stimulation of foliculogenesis in *in vitro* fertilization cycles.

2.1.2.1 Ovarian hypofunction – pathophysiology

When discussing causes of recurrent miscarriages, experts differ in their opinion on the role of luteal insufficiency, the so called implantation factor. This is when a discrepancy occurs between adequate endometrial secretion and high nutritional needs of the fertilized egg, either during its free transport through the uterus before implantation or during histiotrophic nutrition. This discrepancy may lead to a suppression of embryonic development and the pregnancy ends in miscarriage in the first trimester (Erlebacher, 2004).

2.1.2.2 Ovarian hypofunction - diagnosis

During a pre-conception assessment, luteal insufficiency should be considered in patients with very short secretory phase by basal temperature readings, recurrent severe retardation of secretory transformation of the endometrium by microabrasion, or a significant reduction in serum progesterone in the secretory phase of the menstrual cycle (Zwinger, 2004).

2.1.2.3 Ovarian hypofunction - treatmen

No optimal, universal and adequately effective IVF stimulation protocol can be found in the literature (Mardesic, 1995). In these stimulation cycles, higher doses of gonadotropic hormones are usually used and a lower number of oocytes are obtained. Whilst fertilization rate is within the norm, there is significantly lower percentage of obtained clinical pregnancies. With higher incidence of early pregnancy losses (mainly in women above 40 years of age), the percentage of pregnancies ending in a delivery of a healthy foetus in women with reduced ovarian reserve is significantly lower than in dysfertile couples with other than ovarian factors of infertility.

Stimulation protocols in this group of patients should use higher doses of rFSH (max. 300 IU/D), in combination with GnRH antagonists (from 6th DC). Follicular phase of the cycle should not be prolonged because of the risk of premature ovulation and ovulation should be induced by an administration of 10 000 IU hCG when a minimum of 3 follicles ≥ 17mm are visible by UZ folliculometry. Oocytes should be withdrawn no later than 16th day of a menstrual cycle. Embryos obtained through prolonged cultivation and assisted hatching should be transferred under gestagen facilitation of luteal phase no longer than 20th DC. The most reliable and most successful method of achieving pregnancy in POF women is *in vitro* fertilization using a donated oocyte together with oestrogen-gestagen preparation of the endometrium (Hudeček, 2004). Stimulation of ovulation with gonadotropins in women with POF is ineffective. Centres of assisted reproduction report pregnancy rate in women with POF around 40 – 50% per cycle. Even though the child is genetically related to the father only, not to the mother, this method of infertility treatment in women with POF is generally acceptable, especially because the woman has a chance to carry the pregnancy to term herself and is able to breast feed the child (Žáková, 2006). There is about 5% chance in women who do not accept donated oocytes that they are able to get spontaneously pregnant despite the diagnosis of POF. The likelihood of this depends mainly on aetiology of POF (Altchek, 2003).

There are discussions in the literature on utilization of native IVF cycles, protocols with minimum stimulation, including a possibility to convert a stimulation cycle into intrauterine insemination (Shahine, 2009, Schimberni, 2009). Even though these techniques of assisted reproduction show significantly lower efficacy, they may be considered as a treatment option in individual specific cases.

A long-term hormonal therapy leading to pseudopregnancy followed by an administration of gestagens during a subsequent pregnancy (usually during the first trimester) is indicated in patients with luteal insufficiency. Decrease in estrogen receptors as progesterone receptor promoters can be modulated by the means of gestagen substitution (supra-physiological doses of progesterone – 150 mg per day) (Hudeček, 2004).

2.2 Gynaecology-unrelated endocrinopathies

2.2.1 Thyrotoxicosis

Thyrotoxicosis (hyperthyreosis) is a clinical syndrome caused by an overproduction of thyroid hormones. The main signs and symptoms of thyrotoxicosis result from hypermetabolism due to intensified oxidative processes in the body caused by excessive concentrations of these hormones. Graves-Basedow disease is the most frequent form of hyperthyreosis (60-85% of thyrotoxicoses) with a production of anti-thyroid peroxidase autoantibodies and anti-thyrotropin receptor antibodies. Approximately 10 – 30% of hyperthyreoses involve toxic multinodular goitre with autoimmune production of thyroid hormones (T3, T4). Inflammations also frequently cause hyperthyreosis by provoking T3 and T4 secretion (Ďuriš, 2001).

Clinical signs of thyrotoxicosis include nervousness, hand tremor, weight loss with increased appetite, palpitations, heat intolerance and hyperhidrosis. Other subjective symptoms include emotional lability, muscle weakness and diarrhoea.

Objective symptoms include tachycardia or atrial fibrillation, high pulse pressure (the difference between systolic and diastolic pressure), precordial pulsation, and accentuated first sound above the apex of the heart. Gynaecological symptoms include polymenorrhoea, metrorrhagia, sometimes amenorrhoea or sterility. Warm, soft skin, goitre and increased psychomotor reactivity or restlessness may all contribute to the complete clinical picture of hyperthyreosis.

2.2.1.1 Pathophysiology of thyrotoxicosis

Hyperthyreosis might be accompanied by an increased level of gonadotropins, SHBG, estrogens and androgens (although the free fraction of these steroids is lowered due to the increased SHBG levels). A change to the concentration of free steroids and direct effect of thyroid hormones frequently causes anovulation and luteal insufficiency. Hyperthyreosis might be associated with polymenorrhoea and metrorrhagia as well as amenorrhoea and sterility. Some studies have shown that the autoimmune thyroiditis (AT) itself, without obvious or subclinical thyroid gland dysfunction, diagnosed before conception, is associated with infertility, recurring miscarriages and more frequent failure of assisted reproduction methods (Stagnaro-Green , 2004, Poppe 2003).

One theory uses immunological mechanisms to explain the association between infertility and AT without thyroid gland dysfunction (Poppe, 2003). Some published papers identified concurrent occurrence of anti-thyroid and anti-ovarian antibodies; this may contribute to explain the association between AT and ovarian dysfunction (Sterlz, 1997). However, cell immunity is more likely to be responsible for recurring miscarriages. According to this theory, AT is one of the symptoms of a systemic autoimmune disease and represents an indicator of an alteration of the woman's immune system responsible for recurring miscarriages. Elevated levels of CD 5/20 lymphocytes identified in women with AT and an increased risk of miscarriage supports this theory (Roberts, 1996).

2.2.1.2 Diagnosis of thyrotoxicosis

Thyrotoxicosis is diagnosed from the patient's medical history and an assessment of the clinical picture and laboratory parameters. Thyrotoxicosis is characterised by decreased and

even undetectable TSH level and hyperthyroxinemia. TSH levels above 0.1 mU/L exclude a significant form of thyrotoxicosis. An optimal way of treatment should be decided from serum autoantibody levels (anti-thyroid peroxidase autoantibodies, anti-thyrotropin receptor antibodies). Imaging methods and gammagraphy of the thyroid gland are also important (Ďuriš, 2001).

2.2.1.3 Treatment of thyrotoxicosis

Treatment of hyperthyreosis includes lifestyle changes (regular, substantial food intake, avoiding extreme temperatures and excessive physical activity), thyreostatic treatment, subtotal strumectomy and treatment with radioiodine. Pharmacological thyreostatic treatment suppresses the overproduction of thyroid hormones by the thyroid gland. The thiouracil derivatives and carbimazole represent the first line treatment. A surgical treatment, subtotal strumectomy, can be applied when remission was achieved using a thyrostatic agent (florid thyrotoxicosis is a contraindication to any surgery as the patient is at risk of developing thyrotoxic crisis). An administration of a therapeutic dose of radioiodine is indicated when thyrotoxicosis is a co-morbidity to cardiopathy and when thyrotoxicosis recurred following strumectomy (Ďuriš, 2001).

2.2.2 Hypothyreosis

Hypothyreosis is a disorder characterized by decreased thyroid hormone levels. The prevalence of hypothyreosis in the population is about 5-8%, higher in women than men (8:1) and increases with age. Hypothyreosis should always be thought of in older women (prevalence 15 – 20%), not only if the patient presents with specific symptoms but also if they report general complaints such as fatigue, depression and myalgia. Autoimmune thyroid gland disease as well as, understandably, post-thyroidectomy states or treatment with radioiodine are among the most frequent causes. The clinical picture is diverse and includes fatigue, inefficiency, somnolence, depression, poor cold tolerance, weight gain, feeling of pressure on the neck (may also occur if the thyroid gland is not enlarged during AIT), dry skin, myalgia and arthralgia.

The thyroid gland may be enlarged, nodular as well as reduced, thinking and motor functions are slowed down, hypomimia, oedema of the face, eye lid oedema, macroglosy, deep voice. Anaemia is usually normochromic, pernicious in about 10% of cases and associated with autoimmunity, gynaecological symptoms include menstrual cycle disorders, menorrhagia, infertility and galactorrhoea (Brunová, 2008).

2.2.2.1 Pathophysiology of hypothyreosis

Hypothyreosis is one of the most important endocrine primarily non-gyneacological endocrinopaties that affect female fertility. Untreated hypothyreosis reduces fertility, increases the incidence of spontaneous abortions and increases the incidence of premature deliveries (Ďuriš, 2001). Manifest hypothyreosis is frequently linked to anovulation, oligomenorrhoea or amenorrhoea and infertility. Thyroid hormones directly impact on the correct function of oocytes, lutein cells and granulosa cells. In addition, hypothyreosis is associated with a reduction of gonadotropins (particularly the luteinizing hormone) and with an increase in prolactin levels; this results in a decreased production of ovarian steroids. Reduced levels of thyroid hormones result in their reduced production and, consequently, the sex hormone binding globulin (SHBG) levels also decline, the level of free

testosterone increases as does peripheral aromatization of androstendione to estrone (Krassas, 2000). Thyroid hormones are very important for intrauterine foetal development, particularly for the development of the brain and for the development of the hypothalamic-pituitary-thyroid axis. Gravidity represents a period when an increased production of thyroid hormones is required. The foetus depends completely on the mother during the first trimester, and the contribution of the mother to foetal hormonal levels remains significant throughout (maternal productions after birth represent about 30% of thyroxin in the umbilical cord blood) and its importance increases during foetal thyreopathies and insufficient production of thyroid hormones by the foetus. Total production of thyroid hormones in gravidity increases by about 25 – 30% (Karásek, 2007). A tendency to subclinical hypothyreosis during pregnancy was observed in a significant proportion of women with normal free thyroxin and TSH levels. The impact of subclinical or even manifest hypothyreosis during pregnancy on recurrent miscarriages is evidenced by the time when miscarriages occur - usually during the first trimester when the foetus is completely dependent on its mother's production of thyroid hormones (Poppe, 2003).

2.2.2.2 Diagnosis of hypothyreosis

Primary hypothyreosis by increased TSH levels and reduced free T3 and free T4 levels, central hypothyreosis is then characterized by decreased or normal (i.e. not adequately increased) TSH levels (Brunová, 2008).

2.2.2.3 Treatment of hypothyreosis

Treatment of hypothyreosis is initiated with small doses of 25 µg/day and sometimes just 12.5 µg/day of thyroxin. The dose is increased every 7 – 14 days to the expected maintenance dose. The dose is reduced again if the patient poorly tolerates the treatment, i.e. suffers from palpitations, angina pectoris or has signs of heart failure. The demand for thyroid hormone secretion increases during pregnancy and thus thyroxin dose in mothers previously treated for hypothyreosis should be increased during pregnancy by 30% or even 50% (Brunová, 2008).

2.2.3 Diabetes mellitus

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycaemia developing as a result of insulin secretion disorder or as an effect of insulin or a combination of these factors. The main symptom is hyperglycaemia. From biochemical perspective, diabetes influences metabolism of carbohydrates, lipids and proteins. Clinically, it is responsible for the development of microvascular and macrovascular complications associated with organ specific degenerative processes and leading to neuropathic complications (diabetic ketoacidosis, cardiovascular complications, diabetic retinopathy, neuropathy, nephropathy), (Ďuriš, 2001).

Classification of diabetes mellitus:

a. Diabetes mellitus
    1. Type 1 diabetes mellitus - insulin-dependent
    2. Type 2 diabetes mellitus - non-insulin-dependent
    3. Malnutrition-related diabetes mellitus
    4. Other specific types (secondary) of diabetes mellitus – hyperglycaemia associated with another cause (e.g. pancreatic disease, endocrinopathy).

b. Impaired glucose tolerance
c. Gestational diabetes mellitus

2.2.3.1 Pathophysiology of diabetes mellitus

Diabetic female patients are more frequently diagnosed with an ovulatory disorder leading to infertility. A comparison of hormonal profile of diabetic patients suffering from amenorrhoea and women with regular menses suggests different pathophysiological mechanisms, specifically the presence of hyperandrogenism. The effects of hyperinsulinaemia are particularly important. Hyperinsulinaemia stimulates androgenesis in the ovaries. This stimulation is via IGF receptors found in the ovaries present in sufficient amount. This is either a traditional example of the linkage between insulin and steroidogenesis or a hyperreactivity of ovarian receptors for a different reason (Svačina, 1997). According to this theory, changes to pituitary hormones might be secondary, determined by higher level of androgens. Defect of serine phosphorylation with a common manifestation on peripheral insulin receptors, ovaries and adrenal glands represents another significant theory. A slight increase in total testosterone and androstendione levels occur despite concurrent increase in catabolism of androgens. Under normal circumstances, around 66% of the circulating testosterone is bound to the *sex-hormone-binding globulin* (SHBG). When fasting (e.g. anorexia), SHBG concentration increases. On the contrary, SHBG level decreases with increasing BMI, mainly in android obesity and polycystic ovary syndrome (particularly if associated with obesity) and in association with diabetes mellitus; this further increases android hormone concentrations. Hyperinsulinism that is associated with this disease, is one of the possible explanations. Experimental *in vitro* studies show that insulin has an inhibitory effect on SHBG synthesis in the liver (Cogswel, 2001).

Hyperinsulinaemia is diagnosed in as many as 27% of women with a history of habitual abortion (Carrington, 2005) Hyperinsulinaemia influences endometrial functions by reducing the levels of the two main endometrial hormones, glycodelin and IGFBP (insulin-like growth factor binding protein). Hyperinsulinaemia is diagnosed in 40–50% of women with the polycystic ovary syndrome (Kauffman, 2003).

Spontaneous abortion is seen more often in women with decompensated diabetes mellitus (DM) during early pregnancy. It is more frequent in poorly compensated type 1 DM patients, although it is sometimes diagnosed in patients with type 2 DM that had not been diagnosed prior to their pregnancy. Pregnancy is considered a diabetogenic state and the onset of gestational diabetes mellitus is associated with an increased insulin resistance (Hájek, 2004).

Decompensated type 1 diabetic females suffer more frequently from spontaneous abortions (even repeatedly), particularly as a consequence of higher incidence of diabetic embryopathy DE (2-3x more frequent in diabetics in comparison to healthy population). Diabetic embryopathy is a congenital developmental defect or a malformation of the foetus not compatible with life. Etiopathogenesis of DE has not been elucidated yet. Clinical and experimental knowledge confirm that hyperglycaemia is the main metabolic teratogen. Direct link between HbA1c level at the beginning of pregnancy and the incidence of diabetic embryopathy has been confirmed (Ďuriš, 2001).

2.2.3.2 Diagnosis of diabetes mellitus

Diagnosis of diabetes mellitus is made from patient's urine glucose levels and blood testing with oral Glucose Tolerance Testing (oGTT). Prior to conception, current metabolic compensation – glycaemic profile, glycosylated haemoglobin (HbA1C) and diabetic complications assessment – is reviewed. Pregnancy is not recommended in women with severe diabetic organ complications (Hájek, 2004)

2.2.3.3 Treatment of diabetes mellitus

Treatment should focus on supplementing or inhibiting the effects of the relevant hormones and careful diabetes mellitus control (dietary regimen, insulinotherapy).

Classification of DM therapies:

1. Non-pharmacological therapy
   - Patient education
   - Diet
   - Physical activity
2. Pharmacological treatment
   - Insulin (in insulin-dependent type 1 DM and always during pregnancy with any type of diabetes)
   - Oral antidiabetics (non-insulin dependent type 2 DM)

Treatment should be comprehensive, managed by an experienced diabetologist (Ďuriš, 2001). Prescribing metformin, an insulin sensitizer, in women with PCOS represents therapeutic application of an agent with promising effects in the area of anovulation sterility and dysfertility (Višňová, 2003).

2.2.4 Hyperprolactinaemia

Prolactin is a polypeptide hormone synthesised by lactotropic cells of the anterior pituitary. The main effect of this hormone is ensuring adequate postpartum lactation. In collaboration with other hormones, prolactin influences the growth of mammary glands during pregnancy. Prolactin levels in women who do not breast feed decline quickly within two weeks after birth and ovulation is likely to restart within 10 weeks. Hyperprolactinaemia is a disease with a pathological increase in prolactin levels out of postpartum period (Ďuriš, 2001).

2.2.4.1 Pathophysiology of hyperprolactinaemia

Excessive prolactin levels reduce the effects of hypothalamic GnRH and thus normal pulsate secretion of luteinizing hormone and follicle-stimulating hormone. Elevated prolactin levels also have a negative effect on luteinizing hormone increase in the middle of a menstrual cycle (peak LH). Basal levels of gonadotropins are within the norm. Lack of pulsate gonadotropin secretion leads to the functional hypogonadism with anovulation. Anovulation cycles are clinically manifested as oligomenorrhoea or amenorrhoea with subsequent reduction in fertility. The clinical picture typically also includes galactorrhoea, symptoms of estrogen insufficiency (reduced vaginal secretion, osteoporosis), mood swings and hirsutism. Hyperprolactinaemia is found in women with chronic renal insufficiency, with liver cirrhosis and those using certain drugs (psychotropics, antiemetics, antihypertensives, H1 and H2 receptor antagonists). It is found in patients with

hypothalamic disease (cranial and nasopharyngeal irradiation), pituitary disease (tumours – prolactinoma, metastases, meningioma), with primary hypothyreosis or it may be idiopathic (Ďuriš, 2001).

2.2.4.2 Diagnosis of hyperprolactinaemia

The diagnosis of hyperprolactinaemia is made from rigorous medical history, detailed clinical assessment and blood prolactin levels. Prolactin levels above 16 ng/mL are considered as hyperprolactinaemia. Levels exceeding 200 ng/mL suggest prolactinoma, 200 - 500 ng/mL is pathognomonic for prolactinoma and the levels exceeding 1000 ng/mL evidence an invasive tumour expanding to sinus cavernosum. Levels below 100 ng/mL are usually not a symptom of a pituitary tumour (Ďuriš, 2001).

2.2.4.3 Treatment of hyperprolactinaemia

Treatment of hyperprolactinaemia is determined by the primary cause. Surgery, specifically the transsphenoidal hypophysectomy (transcranial approach is required when large macroprolactinomas are treated), is the method of choice for diagnosed microprolactinomas and macroprolactinomas. Radiation therapy is a complementary method in patients with incurable microprolactinomas. Pharmacological treatment is used in patients with hyperprolactinaemia caused by hypothalamo-pituitary dysfunction or in those with idiopathic hyperprolactinaemia. Pharmacological agents used include dopamine agonists that normalize prolactin secretion in about 85 – 90% of patients and reduce the tumour in about 50%. The most frequently used agents include ergoline derivatives bromocryptine, lisuride and terguride (Ďuriš, 2001).

3. Conclusion

A comprehensive and interdisciplinary approach is required to diagnose the causes of habitual miscarriage in a woman. The use of simple and widely available assessment methods in the basic differential diagnosis algorithm is preferred. If these do not provide a clear identification of aetiology of infertility, it is suitable to use more specific and technically demanding techniques. Adequate differential diagnosis enables determination of likely aetiology and a use of an appropriately targeted therapy.

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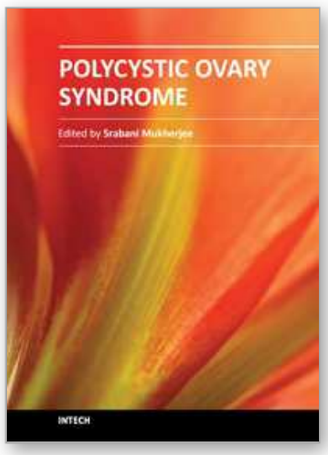

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Brought into the limelight many decades ago, Polycystic Ovary Syndrome (PCOS) is still, to date, surrounded by controversy and mystery. Much attention has been attracted to various topics associated with PCOS research and there has been a healthy advance towards bettering the understanding of the many implications of this complex syndrome. A variety of topics have been dealt with by a panel of authors and compiled in this book. They span methods of diagnosis, reproductive anomalies, metabolic consequences, psychological mindset and ameliorative effects of various lifestyle and medical management options. These books are designed to update all associated professionals on the recent developments in this fast-growing field and to encourage further research into this thought-provoking subject.

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