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The Impact of Polycystic Ovarian Syndrome on Gestational Diabetes

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1. Introduction

When Stein and Leventhal, in 1935, observed a group of women who suffered from sterility, oligomenorrhoea, or amenorhhoea, hirsutism, and enlarged polycystic ovaries, the disorder that became known as the polycystic ovarian syndrome (PCOS) or the Stein-Leventhal syndrome, was diagnosed for the first time (Stein, 1958). The variability of individual presentation, as well as a varying collection of signs and characteristic features, with no single diagnostic test justify the categorization of the PCOS as a syndrome that affects not only reproductive health, but also the metabolic and cardiovascular systems. Although PCOS is one of the most common endocrinopathies in women, with an incidence of about 5-10% throughout the reproductive age span (Metalliotakis, 2006), there are divergent opinions about how to define and diagnose PCOS, as well as different types of treatment options throughout Europe and the US (Badawy & Elnashar, 2011). The high prevalence of women with this endocrine disorder highlights the importance of understanding the clinical presentation, pathophysiology, associated disorders, and treatment options. Up to 40% of women of reproductive age with PCOS have Type 2 diabetes or an impaired glucose tolerance (Legro et al., 2005), a form of insulin resistance that occurs equally in obese, normal weight, and thin women with PCOS (Matalliotakis et al., 2006). PCOS has been associated with an increased risk for gestational diabetes mellitus (GDM), but solid evidence confirming PCOS as a risk factor for GDM is still missing (Toulis et al., 2009). GDM, a well-known state of carbohydrate intolerance with a high, and rising, prevalence, causes not only maternal but also fetal pregnancy complications. GDM has a presentation similar to PCOS, and both are considered risk factors for Type 2 diabetes mellitus (Retnakaran et al., 2008).
The aim of this review is to summarize the available evidence about the risk of impaired glucose tolerance and GDM in PCOS women, as well as to review the pathophysiological aspects. In addition, the potential beneficial influence of several PCOS-specific treatment options on PCOS and GDM will be discussed.

2. Diagnostic criteria for polycystic ovary syndrome

The National Institutes of Health (NIH) has published criteria for diagnosing PCOS, based on an international conference on PCOS held in 1990. Accordingly, diagnostic criteria for the syndrome includes chronic anovulation, combined with clinical or biochemical

hyperandrogenism, where other causes have been excluded (diagnosis of exclusion) (Huang et al. 2010). An expanded definition can be found in the revised Rotterdam criteria, a consensus on diagnostic criteria of the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology. At least two of three criteria must be present: (i) oligoamenorrhoea or amenorrhoea; (ii) hyperandrogenism (clinical/biochemical); and (iii) polycystic ovaries on ultrasound, defined as more than 12 cysts of 2-9mm, or >10ml volume (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The revised Rotterdam criteria are considered the current standard diagnostic criteria.

In 2006, the Androgen Excess Society (AES) attempted to define evidence-based guidelines for diagnosis and future research in a review (Azziz et al., 2006). The AES task force suggested that androgen excess must be considered a central feature of the disease, and that PCOS should be defined by the presence of hyperandrogenism (clinical and/or biochemical) together with signs of ovarian dysfunction (oligoovulation or anovulation and/or polycystic ovaries), where similar disorders have been excluded (Azziz et al., 2006). Conditions for exclusion must be clarified in the diagnostic procedure. Premature ovarian failure with oligo-/amenorrhea that might be associated with other autoimmune endocrinopathies, hyperprolactinoma, or Cushing's syndrome are a few clinical possibilities that merit attention.

3. Pathophysiologic aspects of polycystic ovary syndrome

The heterogeneity of the syndrome and the unclear etiology favor the theory of multiple underlying pathophysiologic mechanisms that have yet to be fully elucidated. A heritable etiology for PCOS has been investigated intensively and several associated polymorphisms have been identified. However, to date, none of the possible candidate genes (e.g., regulators of the microbiological action of insulin) could be correlated with the onset of PCOS (Dumesic et al., 2007). In the research field of PCOS, studies on polymorphisms gained on importance within the last years. Moreover, environmental factors (e.g.: lifestyle, nutrition) together with certain genetic mutations might lead to the individual manifestation of PCOS but the diversity of clinical presentations aggravates the identification of genes involved in the origin of PCOS.

Although the definition of “polycystic ovary syndrome” might be ambiguous, it is important to emphasize that polycystic ovaries need not be present to diagnose this syndrome. Nevertheless, PCOS patients who demonstrate ovaries with multiple subcortical cysts on ultrasound and an increased proportion of primary follicles (Dumesic et al., 2007) have a greater rate of hyperandrogenism than women with PCOS without abnormal follicle development. The presence of polycystic ovaries might indicate a major clinical alteration of PCOS, and the presence of polycystic ovaries in childhood has been suggested as an indicator of a genetic predisposition (Battaglia et al., 2002). Moreover, an abnormal autoimmune history has been considered in PCOS, in which functional autoantibodies might favor the development of PCOS (Ott et al., 2010, Gleicher et al., 2007). Assuming a relation between insulin resistance, ovarian function, and thyroid function, elevated antiTPO levels have been found to influence treatment response in women with PCOS and infertility (Ott et al., 2010). Notably, PCOS has been called a marker for “reduced ovarian aging,” since serum anti-Müller hormone (AMH) levels are higher in anovulatory women and have been found to be elevated in women with PCOS. AMH concentrations correspond

to the number of antral follicles and can be correlated to the level of ovarian dysfunction in infertility. Thus, it is possible that the process leading to ovarian aging is delayed in PCOS, which might also lead to a later onset of menopause in these women (Mulders et al., 2004).
Three hypotheses are frequently discussed in literature about how defects in primary cellular control mechanisms might result in PCOS: (i) an elevated luteinizing hormone (LH) pulse frequency and amplitude, and relatively low follicle stimulating hormone (FSH) serum levels (LH+/FSH-) lead to anovulation and ovarian hyperandrogenism; (ii) a defect in the sex steroid metabolism within the ovaries (theca cells) causes an exaggerated ovarian androgen secretion; and (iii) a regulatory dysfunction of the insulin pathway results in hyperinsulinemia and insulin resistance and contributes to the development of PCOS (Franks et al., 1998). These pathophysiologic mechanisms might be of special interest regarding the risk for GDM. Indeed, several possible insulin-mediated pathways have been identified that might contribute to hyperandrogenism in PCOS patients (see Figure 1).

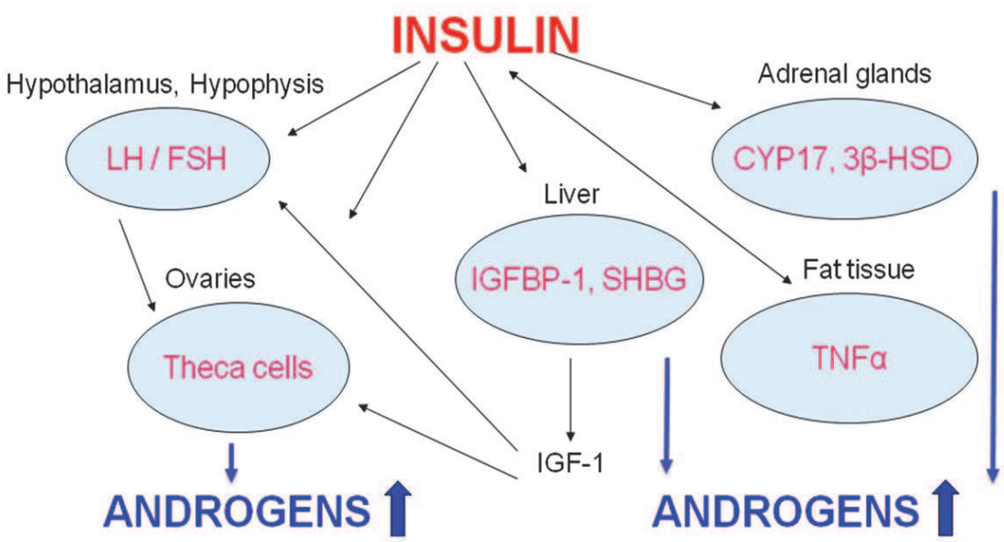

Fig. 1. How increased insulin levels might contribute to hyperandrogenism

These pathophysiologic hypotheses are related in a variety of ways. Elevated hypothalamic gonadotropin-releasing hormone (GnRH) pulsatility influences LH secretion; consequently, dysfunctional pulse frequency and amplitude lead to an increased 24-hour secretion of LH. High LH combined with high levels of insulin result in increased ovarian androgen production. Hypersecretion of LH also affects oocyte development. A defect in androgen synthesis that results in an increased enzymatic activity involved in the synthesis of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androstenedione leads, consequently, to an inadequate production of testosterone in ovarian theca cells. The synergistic interaction between LH and insulin on the ovarian theca cells leads to stimulation of androgen production. Several studies have provided useful information about a correlation between hyperandrogenism and a state of increased insulin resistance (Balen, 2004) (Baptiste et al., 2010). In women with PCOS, an another cause of high androgen levels can be explained by the influence of compensatory hyperinsulinemia

on the hepatic synthesis and secretion of the sex hormone-binding globulin (SHBG). SHBG levels are reduced and the blood concentrations of biologically active androgens are thus increased. In addition, it has been suggested that adipose tissue dysfunction also plays a central role in the metabolic and endocrine abnormalities observed in PCOS (Villa J et al., 2011).

4. Clinical manifestation of polycystic ovary syndrome

A variety of signs and symptoms can be found in women who suffer from PCOS in which ovarian hyperandrogenism is considered the cardinal characteristic. The variable clinical presentation includes gynecological symptoms that include dysfunctional menstrual bleeding, such as oligo- or amenorrhea, or any kind of abnormal uterine bleeding combined with infrequent or absent ovulation, infertility resulting from elevated androgen levels, and polycystic ovaries (Dumesic et al., 2007). With regard to gynecologic malignancies, chronic anovulation over a long period of time is associated with a higher risk of developing endometrial adenocarcinoma and a higher incidence of endometrial hyperplasia, compared to age-matched controls (Badawy & Elnashar, 2011). Elevated serum androgen levels lead to androgenic disorders, such as acne, hirsutism, and alopecia androgenica, where hyperandrogenism is differently expressed in the PCOS phenotypes, resulting in cosmetic issues and psychological effects that can be burdensome and difficult to cope with.

Last not least, PCOS has been considered to be associated with a increased risks for type II diabetes mellitus and GDM. When considering the association with GDM, it is notable that both PCOS and GDM share some common characteristic features, including obesity, increased insulin resistance, dyslipidemia, and other metabolic abnormalities. The common presence of lipid abnormalities, such as elevated serum triglyceride- and low-density lipoprotein levels due to negative hormonal influences on the lipid homeostasis coexist with obesity and increased insulin resistance. PCOS shares components with the metabolic syndrome characterized by a combination of insulin resistance, dyslipidemia, and hypertension (Boomsma et al., 2006). Although a high BMI is associated with a higher risk of arterial disease, an increased cardiovascular risk (up to two-fold) in women with PCOS cannot be completely ascribed to a higher BMI (de Groot et al., 2011). Obesity and PCOS show, on the one hand, an independent influence, but, on the other hand, seem to have additive adverse effects on insulin action.

Up to 50% of women with PCOS suffer from an imbalance in carbohydrate homeostasis, central fat deposition, and increasing insulin resistance during pregnancy (Huang et al., 2010). It has been estimated that 25–70% of women with PCOS show a rise in insulin resistance and have an increased risk of developing complications during pregnancy, first and foremost of which is GDM (Godoy-Matos et al., 2009).

5. The risk of gestational diabetes in women with polycystic ovary syndrome

GDM is defined as the onset or first recognition and diagnosis of glucose intolerance during pregnancy. The diagnostic criterion for GDM is the 75g, two-hour oral glucose tolerance test (OGTT).

In fact, recent meta-analyses of pregnancy outcomes in women with PCOS demonstrated a significantly higher chance of developing GDM for PCOS women (odds ratios of about 2.90) (Boomsma et al., 2006) (Toulis et al., 2009). However, when analyzing the available evidence

separately, there were largely conflicting results: while most of the studies demonstrated an increased risk for GDM in PCOS women (odds ratios ranging from 1.15 to 22.15) (Wortsman et al., 1991 as cited in Boomsma et al., 2006) (Radon et al., 1999, as cited in Boomsma et al., 2006), a few found odds ratios from 0.31 to 0.96 (Turhan et al., 2003, as cited in Boomsma et al., 2006) (Haakova et al., as cited in Boomsma et al., 2006). A comparison between the study designs revealed that the increased risks were predominantly found in cohort studies rather than in case-control studies. In addition, meta-analyses revealed a significant heterogeneity between the analyzed studies.

Conversely, some studies did not seem to support a higher prevalence and previous history of PCOS in women diagnosed with GDM, when compared to pregnancies in women with normal glucose homeostasis (Wijeyaratne et al., 2006) (Kousta et al., 2000). Obesity, PCOS, and diabetes in first-degree relatives have been described as risk factors for developing GDM and gestational impaired glucose tolerance, especially in young women and teenage pregnancies (<20 years) (Karcaaltincaba et al., 2011).

All in all, there is no solid evidence proving the increased risk for GDM in PCOS patients, but a trend assuming that the risk is, indeed, increased in women with PCOS, is recognizable. Confronted with the wide clinical and pathophysiological spectrum associated with the syndrome, further studies are warranted to validate the existing data.

5.1 Diagnostic aspects

The guidelines developed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) consider a screening for pre-gestational diabetes in high-risk women at the first prenatal visit and universal screening between the 24th and 28th week of gestation (Holt et al., 2011). In daily routine, an OGTT is performed in the third trimester. According to the diagnostic recommendations published in March 2010 by the IADPSG, fasting blood glucose concentrations that exceed 92 mg/dl, one-hour and two-hour glucose levels of more than 180 mg/dl, or 153 mg/dl measured during the OGTT, lead to the diagnosis of GDM (Metzger et al., 2010). Increased measurements in each of the three values raise the possibility of an adverse pregnancy outcome. A benefit of generalized testing to evaluate glycaemia levels in all pregnant women before the usual window is still a subject of controversy in the literature and must be decided individually (Karagiannis et al., 2010, Hadar et al., 2009). If increased levels of glucose are found in urine samples, or if GDM was present in a previous pregnancy, an OGTT in the second trimester should be performed. Since women who suffer from PCOS are considered to be at higher risk for developing GDM, it could be argued that they should undergo a more detailed and earlier screening for GDM.

5.2 Pathophysiological hypotheses about the risk of gestational diabetes in women with polycystic ovary syndrome

Several pathophysiologic mechanisms have been discussed that might contribute to the phenomenon of the increased GDM risk associated with PCOS.

5.2.1 Genetic predisposition

It has been hypothesized that a particular genetic background could contribute to the association between PCOS and GDM. In women with familial partial lipodystrophy due to LMNA (lamin A/C) mutations, a rare disorder characterized by a selective loss of adipose

tissue and insulin resistance, the prevalence of PCOS and gestational diabetes was found to be higher than in the general population (Vantyghem et al., 2008). Moreover, mutations of the VNTR (variable number of tandem repeats) locus, upstream of the insulin gene (INS) where insulin expression is regulated, have been found in both women who suffer from PCOS and in women with GDM (Waterworth et al., 1997) (Lambrinoudaki et al., 2010).

5.2.2 Preexisting insulin resistance

In pregnancy, rising blood levels of lipolytic placental hormones lead to an elevation of free fatty acids that are commonly associated with the development of a dose-dependent insulin resistance. Affecting skeletal muscle glucose uptake, free fatty acids create a state of local insulin resistance and, as concentrations are elevated in late pregnancy, an increase in tissue insulin resistance can be observed during pregnancy (Sivan & Boden, 2003). In the presence of PCOS and a preexisting state of increased insulin resistance accompanying the syndrome, hyperglycemia seems to be induced more easily. The high pre-conception insulin resistance might have a deleterious additive effect on pancreatic beta cells, which are incapable of coping with the additive physiological insulin resistance of pregnancy (Khattab et al., 2011), thereby leading to an increased incidence of GDM (Toulis et al., 2009).

5.2.3 SHBG levels

Hyperinsulinemia stimulates in much the same way as LH-agonist ovarian testosterone production and decreases the serum sex hormone-binding globulin (SHBG) concentration. SHBG is known to have biologic functions beyond the regulation of free estrogen and testosterone serum levels. It has also been emphasized that low SHBG levels are associated with a minor glucose tolerance, thus, attributing a role to these low SHBG levels in the maintenance of glucose homeostasis. A possible explanation might be a modulation of the biologic effects of both estrogen and testosterone on liver, fat, and muscle tissue, as well as on other peripheral tissues (Ding et al., 2009). Furthermore, low plasma SHBG levels has been suggested as predictive for the risk of developing Type 2 diabetes mellitus (Ding et al., 2009). As an early indicator of GDM risk, low preconception levels of SHBG concentrations have been identified as strong predictors in PCOS women, independently of obesity and measures of insulin resistance. One study suggested that assessment of SHBG levels before conception might be a useful tool to by which to identify PCOS patients at risk for GDM during pregnancy (Veltman-Verhulst et al., 2010). However, the pathophysiologic pathways of this effect are unknown. It remains unclear whether the association between GDM and SHBG is direct or indirect. A lower SHBG results in higher free androgens that have already been demonstrated to be associated with an increased GDM risk (Bartha et al., 2000).

5.2.4 Insulin-like growth factor and insulin-like growth factor binding protein-1

The risk for GDM has been connected to maternal plasma concentrations of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-1 (IGFBP-1), suggesting that these determinants of glucose homeostasis play a potential role in the pathophysiologic process and contribute to the development of GDM (Qiu et al., 2005). Increased serum insulin concentrations lead to an inhibition of IGFBP-1 production, resulting in elevated serum levels of free IGF-1. A recent meta analysis on the interaction between IGFBP-1 and PCOS described lower levels of IGFBP-1 in affected patients (Kelly et al. 2011). Notably, a lower risk for developing GDM was correlated with increased levels of

free IGF-1 and IGFBP-1, where higher C-peptide levels were positively associated with the development of GDM (Qiu et al., 2005). It should be emphasized that lower levels were found in obese women with/or without PCOS, compared to normal weight controls, suggesting that body weight has a certain influence on serum IGFBP-1 levels. The physiologic processes underlying the role of IGF-1 in glucose regulation are unclear. Infusions of IGF-1 are known to suppress glucose counter-regulatory hormones, such as glucagon and growth hormone (Jones & Clemmons, 1995). IGF-1 may also contribute to changes in insulin sensitivity and glucose uptake via direct IGF receptor-mediated effects on skeletal muscle (Sjogren et al., 2001). Alterations in IGFBP-1 concentrations may be due to variations in insulin secretion or hepatic insulin sensitivity, both known to be important factors in glucose regulation (Lee et al., 1997).

5.2.5 The influence of infertility treatments

PCOS is often accompanied by infertility that necessitates ovulation induction, using clomiphene citrate, gonadotropins, or even *in vitro* fertilization (IVF) (Boomsma et al., 2006). These treatment methods are known to increase the incidence of multiple pregnancies, as well as some negative consequences, including a rise in the risk for GDM (Schwartz et al., 1999). Furthermore, pregnancies established after IVF carry an increased risk for maternal complications (Pinborg et al., 2004) (Shevell et al., 2005). However, the increased risk of developing GDM has been suggested to occur independently of obesity, as well as in populations without assisted reproductive techniques (Boomsma et al., 2006) (Toulis et al., 2009).

6. Therapeutic considerations

The therapeutic challenges in the treatment of women with PCOS and GDM or impaired glucose tolerance arise from the diversity of recommendations and research conclusions. If adequately managed, the incidence of adverse perinatal outcomes in PCOS patients who develop GDM was found to be not significantly elevated (Li et al., 2010). Several treatment options exist for each of the symptoms of PCOS, and management of these patients depends on the individual symptoms. Clinical management of PCOS involves risk assessment for metabolic disorders, as diabetes and dyslipidemia, and for hypertension, cardiovascular complications, and liver diseases (Setji & Brown, 2007). Insulin-sensitizing drugs, such as metformin and/or oral contraceptives, are thought to improve the clinical features of PCOS, but limited data is available that assesses the true influence and safety of these drugs in this population (Setji & Brown, 2007). Targeting androgen symptoms, such as acne, hirsutism, and alopecia androgenica, estrogen-containing oral contraceptives, antiandrogens and topical agents are considered first-line therapy for women who do not want to conceive, as they effectively reduce serum androgen levels. In addition, treatment with oral contraceptives is associated with an improvement in the menstrual pattern. However, when trying to achieve pregnancy, other treatment options are offered to the patient. All of these might also independently influence the risk for GDM.

6.1 Lifestyle modifications

Addressing life-style factors before conception should be the first-line approach to reduce any further therapeutic strategies during pregnancy. The appearance of the varying

phenotypes of PCOS depends, to a great extent, on lifestyle and environmental factors (Garruti et al., 2009). Reducing weight improves the endocrine profile and has the most significant impact on the likelihood of ovulation and pregnancy, the most relevant endpoints in infertile PCOS women. Dietary composition has been considered to improve the initial metabolic and reproductive situation in these patients. It has been suggested that low fat diets be recommended to these patients to produce a decrease in hyperinsulinemia (Reaven, 2005). Since it has been well-established that obesity is not only associated with anovulation, infertility, and early miscarriage, but also with late pregnancy complications in women with PCOS (Badawy & Elnashar, 2011), lifestyle modifications, including dietary recommendations and increased exercise in order to achieve weight reduction, should be recommended to these patients. Bariatric surgery has also been advocated as a possible strategy for weight loss in PCOS women, at least in the morbidly obese, and is effective in restoring ovulation and improving insulin resistance. Reducing weight, along with lifestyle modifications that affect the patients' behavior in a continuing way, is considered the most relevant therapeutic approach in women with PCOS (Hirschberg, 2009). Whether it affects the risk of developing GDM in subsequent pregnancies remains an open question (Escobar-Morreale et al., 2005).

6.2 Insulin-sensitizing drugs

Elevated insulin resistance plays an important part in the pathophysiology of PCOS and GDM. Insulin-sensitizing drugs, particularly metformin, are thought to reduce androgen symptoms, positively influence reproductive deregulations (oligo-amenorrhoe, anovulation), and increase pregnancy rates in PCOS patients (Dunaif, 2008). Large placebo-controlled trials are available only for metformin, as this is the only insulin-sensitizing drug with extensive clinical use in women with PCOS (De Leo et al., 2003).

6.2.1 Metformin as a PCOS-specific therapy

Metformin, a biguanide (see Figure 2), is a therapeutic option for restoration of ovulation in PCOS women. Moreover, several studies have suggested metformin as a promising medication in pregnancy in order to reduce the incidence of developing GDM and to minimize the risk for an adverse pregnancy outcome (Carlsen & Vanky, 2010). A variety of studies have been performed to determine the beneficial effects of metformin in PCOS, although the mechanisms of action–a broad spectrum of endocrine, metabolic, vascular, and even anti-inflammatory effects–of this drug have not been completely clarified, as yet (Khattab et al., 2011).

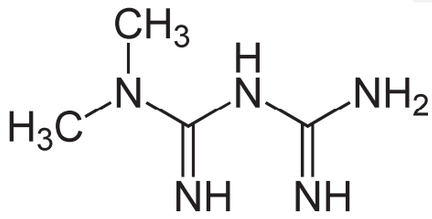

Fig. 2. Formula of metformin

Metformin affects the hepatic glucose output and the insulin-mediated glucose consumption in peripheral tissues, and suppresses the free fatty acid concentrations, which results in a lower substrate level for gluconeogenesis. Metformin improves insulin sensitivity and reduces insulin blood levels by increasing peripheral glucose utilization without negatively influencing normal blood glucose concentrations. With regard to pregnancy, a positive impact on uterine vascularity and blood flow and a reduction in plasma endothelin-1 levels, as well as androgen and LH concentrations, have been mentioned, suggesting that metformin is a possible positive therapeutic drug in the prevention of pregnancy complications in PCOS (Khattab et al., 2011). Thus, it has been assumed that metformin treatment combined with a special diet reduces pregnancy complications, and also prevents the fetus from elevated androgen concentrations (Glueck et al., 2004a).

Several studies have investigated a possible beneficial effect of metformin in the pregnancies of PCOS patients, particularly with regard to the risk of GDM. Some trials even report about a nine-fold (Begum et al., 2009) or ten-fold reduction (Glueck et al., 2002) of GDM after metformin treatment throughout pregnancy. However, the literature is controversial. The anticipated reduction in the prevalence of GDM after treatment with metformin during pregnancy could not be verified in randomized controlled trials, although metformin therapy had improved insulin sensitivity (Legro et al., 2007) (Fougner et al., 2008). In particular, recent large randomized controlled studies and meta analyses could not verify a relevant reduction of pregnancy complications due to metformin treatment (Vanky et al., 2010). Thus, the general use of metformin during pregnancy in non-diabetic women with PCOS cannot be recommended.

Metformin is associated with low gastrointestinal disturbances, but the available trials did not describe any serious adverse events. Classified as a category B drug in pregnancy, metformin appears to be non-teratogenic (Glueck et al., 2004b). However, results from placebo-controlled trials on maternal and fetal health risk have not yet been clarified. The pathogenesis of PCOS has been related to increased intrauterine androgen exposure; thus, the effect of therapeutic investigations on maternal and fetal hormone levels must be considered when treating pregnant women with PCOS. metformin seems to pass the placental barrier and was found to be present in the fetal circulation. However, androgen and estrogen levels did not seem to be influenced and remained within normal range (Carlsen & Vanky, 2010), whereas elevated SHBG levels have been reported in newborns after intrauterine metformin exposure (Vanky et al., 2005). The clinical relevance of these findings remains unclear.

6.3 Other methods of ovulation induction

With regard to pregnancy outcome, there are different possibilities of infertility treatment in women with PCOS and ovulatory dysfunction. Pregnancy induction by assisted reproductive techniques (ART) is offered if women fail to conceive spontaneously. Ovulation induction is based on two principles: (i) ovaries are exposed to a higher level of follicle stimulating hormone; and/or (ii) hormonal derangements are corrected. After exclusion of other causes of infertility, the fertility medication, clomiphen citrate (CC), is considered the first-line therapeutic approach to ovulation induction. In this approach, the development of a single ovulatory follicle is the main goal, since the risk for multiple pregnancies has to be kept as low as possible.

Literature on the risk for GDM as it relates to CC stimulation is scarce. To date, only one retrospective study has been published that compared the effects of CC stimulation and

laparoscopic ovarian drilling in women pre-treated with metformin to those treated with metformin only. For all groups, there was a rate of GDM of about 30%, suggesting that neither CC stimulation nor laparoscopic ovarian drilling exert any effect on the risk for GDM (Ott et al., 2010).

For CC-resistant anovulatory PCOS patients, second-line therapeutic approaches include laparoscopic ovarian drilling and gonadotropin stimulation (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). As mentioned above, only one trial has evaluated whether laparoscopic ovarian drilling would alter the risk for GDM and found no influence (Ott et al., 2010). Whether gonadotropin stimulation is associated with an increased rate of GDM remains controversial. While some studies found no difference in the prevalence of GDM between PCOS patients and controls (Vollenhoven et al., 2000), data from prospective studies suggest that medicamentous ovulation induction leads to an increased risk for GDM (Shevell et al., 2005).

When all of these treatment options fail, IVF remains the last option by which to achieve pregnancy (Badawy & Elnashar, 2011). It has been reported that the prevalence of GDM is substantially increased in women after pregnancy induction via ART than in PCOS patients who conceive spontaneously (Bals-Pratsch et al., 2011). Proceeding on the assumption of a - possibly genetically determined - highly deranged insulin metabolism that may lead to this state of infertility where women cannot conceive spontaneously or with the help of lower-dose stimulation protocols, the higher rate of GDM could be explained. One might raise the question whether the maternal endocrine status before placentation and/or after IVF stimulation possibly influences glucose tolerance in women with PCOS. Furthermore, elevated estrogen levels lead to an excessive stimulation of estrogen receptor alpha in the pancreatic beta cells, producing exaggerated insulin signaling that may cause an increased state of insulin resistance in peripheral tissues (Nadal et al., 2009).

Moreover, IVF is known to lead to an increased risk for maternal complications, including GDM independently of the presence of PCOS (Pinborg et al., 2004) (Shevell et al., 2005). When IVF stimulation is complicated by ovarian hyperstimulation syndrome (OHSS), the risk for GDM increases even more (Raziel et al., 2009). Notably, PCOS is a known risk factor for the development of OHSS. Higher rates of GDM, but also placental abruption prematurity and low birth weight have been reported for pregnancies complicated by severe OHSS. Therefore, these pregnancies should be considered high-risk pregnancies, and followed/treated as such. The best option to prevent OHSS is to use mild stimulation protocols (Raziel et al., (2009). However, metformin has also been mentioned as leading to a significant reduction in OHSS rates (Khattab et al., 2006).

7. Perinatal outcome of women with polycystic ovary syndrome and gestational diabetes

Hyperglycemia negatively influences not only maternal, but also fetal health. Obesity, fertility treatments, and other characteristics of patients with PCOS are associated with a higher incidence of pregnancy complications, such as hypertension and preeclampsia (Boomsma et al., 2008). Compared to normal pregnancies, PCOS patients demonstrate a higher incidence of early pregnancy loss (Li et al., 2010). Likewise, perinatal mortality seems to be increased among women with PCOS, and neonatal complications are observed more frequently (Boomsma et al., 2006). A potential additive effect of co-existent PCOS and GDM on obstetrical complications advocates for a closer antenatal and intrapartal monitoring of

these patients (Alshammari et al., 2010). According to the Barker hypothesis, an altered maternal nutrition and metabolism is thought to lead both to an altered fetal nutrition and to changes in the endocrine and metabolic environment in which the fetus develops (de Boo & Harding 2006). This explains why PCOS complications might affect the fetus.

Maternal glucose levels correlate with fetal birth weight, development of fetal macrosomia, fetal hyperinsulinemia, and fetal body-fat percentage (Yang et al., 2002) (Metzger et al., 2010). Cesarean section is performed more frequently in women with GDM, as the diagnosis "large for gestational age" due to elevated maternal glucose levels is associated with a higher incidence of adverse pregnancy outcomes in spontaneous delivery (e.g., shoulder dystocia). PCOS also seems to correlate with a lower rate of vaginal delivery compared to healthy controls (Bjercke et al., 2002), although the higher incidence of Caesarean sections correlates with the occurrence of obesity, since women with a normal BMI and PCOS have an incidence of Caesarean section equal to that of age-matched controls (Boomsma et al., 2006).

Accordingly, the perinatal outcome of women with PCOS who develop GDM has been investigated intensively within the last several years. Both PCOS and associated factors, such as obesity or the treatment methods for fertility induction, can be considered responsible for the poorer pregnancy outcomes (Thatcher & Jackson, 2006, Boomsma et al., 2008). However, with regard to the risk of macrosomia, preeclampsia, neonatal complications, neonatal anomalies, and death of the fetus in women with GDM and PCOS, compared to women with GDM alone, no significant differences have been observed (Li et al., 2010). Manifest obesity before pregnancy and total weight gain during pregnancy must be closely monitored and addressed insistently, not only to minimize the risk for GDM, but also to achieve better global well-being in women with PCOS.

8. Conclusion and future research areas

The diverse observations regarding the elevated risk of GDM in women with PCOS have presented scientists and clinicians with a challenge. Caution is advised when interpreting clinical and statistical heterogeneous studies on PCOS and pregnancy complications, as a variety of contradictory results are present throughout the literature. The diagnosis of PCOS is inconsistent, as some investigators use only ultrasound criteria alone, and others rely on hormonal or clinical parameters, whereas the revised Rotterdam criteria are considered the current valid diagnostic criteria for the diagnosis of PCOS.

Women with PCOS who want to have children must be informed about the increased risk for developing GDM in their pregnancies. Metabolic findings in PCOS include increased insulin resistance, dyslipidemia, and elevated androgen levels - often accompanied by infertility and infertility treatments in order to achieve pregnancy. Confounding factors, such as obesity and the diverse ovulation induction treatments in infertile women with PCOS, can be considered potentially risk-increasing variables. Those coexisting factors, together with additional predisposing factors, such as a positive family history for diabetes mellitus, have been suggested to correlate with a generally increased risk for developing GDM and impaired glucose tolerance (Toulis et al., 2009).

Comparable pathophysiological mechanisms of insulin resistance and impaired glucose tolerance can be found in GDM and in women with PCOS who demonstrate an increased tissue resistance to insulin. However, the exact pathophysiologic link between PCOS and GDM has not yet been fully elucidated. Future scientific research could aim to clarify the

association between PCOS and GDM and shed some new light on the possible underlying pathomechanisms. Moreover, further investigations to evaluate a potential benefit of early GDM screening are warranted, particularly as GDM is a well-known risk factor for fetal and maternal complications (Tieu et al., 2010).

The presence of increased glucose levels might lead to considerable pregnancy complications and stress on the mother and fetus. Accurate screening for GDM, together with regular consultations and monitoring, as well as addressing additional preventable stress factors, reduce the risk for developing GDM. Primary prevention can be further improved by lifestyle modification in women with PCOS. With regard to early diagnosis, screening in PCOS patients with a variety of risk factors might be justified. One might focus on the development of alternative markers to identify a woman at risk for developing GDM, in addition to the available parameters, such as fasting plasma glucose and OGTT, which enable clinicians to select patients at risk even before the manifestation of GDM. Thus, such markers as androgen levels, SHBG levels, fasting insulin levels, baseline proinsulin levels, and the hip-waist ratio might be of future interest.

Metformin has been highlighted as a promising substance for reducing the risk of GDM in PCOS patients. However, a relevant reduction of obstetrical complications due to metformin treatment could not be verified in a recent randomized and controlled multicenter study (Vanky et al., 2010). The general use of metformin during pregnancy in non-diabetic women with PCOS cannot be considered a valid recommendation.

Even with all the evidence and comparative studies, PCOS, still remains a challenging diagnostic and research issue, particularly with regard to its impact on GDM.

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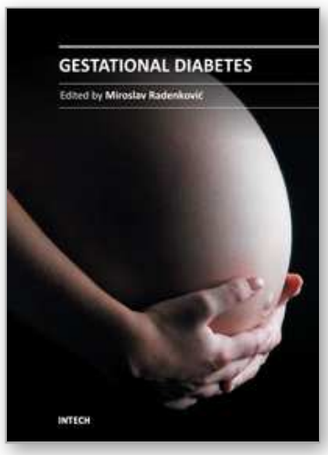

Gestational Diabetes

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Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

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