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Implications of Insulin Resistance / Hyperinsulinemia on Reproductive Function in Infertile Women with Polycystic Ovary Syndrome

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1. Introduction

One of the most common reproductive endocrine diseases that impact many young women worldwide is polycystic ovary syndrome (PCOS). This hormonal problem affects 4 – 18% of women of reproductive age exhibiting various symptoms, such as irregular menstruation, hirsutism, infertility and metabolic disorders (LJ. Moran, et al. 2011). These symptoms in PCOS women are strongly correlated with overweight and obesity. Also, women with PCOS are likely to have metabolic disorders, such as abnormality of glucose and lipid metabolisms that are inevitably involved in diabetes mellitus and coronary artery diseases, respectively (ML. Traub, 2011). Concerning metabolic syndrome in young women, abnormalities in glucose metabolism are seen earlier than dyslipidemia as the initial manifestation; thus, glucose metabolism is suggested to be evaluated first (A. Fulghesu, et al. 2011). Insulin resistance / hyperinsulinemia is frequently associated with 40-50 % of women having PCOS, especially obese women (JE. Nestler, et al. 2002). Furthermore, obese women with PCOS are more likely indicative of insulin resistance than lean women with or without PCOS (P. Acien, et al. 1999). It is well-known that insulin resistance manifests in glucose tolerance test (GTT) prior to diabetes mellitus and coronary artery diseases (ML. Traub, 2011). Based on the recent reports, insulin resistance / hyperinsulinemia correlates with implantation disturbances and causes infertility in PCOS women (DJ, Jakubowicz, et al. 2001). Also, it is reported that the rate of early pregnancy loss is higher in women with PCOS than in normal women (DJ. Jakubowicz, et al. 2002). Thereby, insulin resistance / hyperinsulinemia is strongly linked to women with PCOS and this correlation has to be studied in details. As for obesity and overweight, which also strongly relates with PCOS, body mass index (BMI) is suggested to contribute to severity while assessing many problems, such as miscarriage, anovulation, infertility and increased prevalence of diabetes mellitus (JX. Wang et al. 2002; RJ. Norman, et al. 2002). Also, weight reduction is effective to

improve the PCOS symptoms in obese and overweight infertile women, and insulin sensitizing drug, such as metformin, ameliorates menstrual cycle and ovulation in PCOS women (J. Vrbikova, et al. 2002; B. Baysal, et al. 2001; R. Fleming, et al. 2002). From the above-mentioned facts, the adverse effects of insulin resistance / hyperinsulinemia are inextricable with infertile women with PCOS and cause ovulatory disturbance, implantation failure and early pregnancy loss (in early stage). Yet, the lifestyle changes, such as weight reduction and dietary modification, as well as the use of insulin sensitizing agents are crucial for the improvement of reproductive functions for PCOS women.

2. Insulin resistance / hyperinsulinemia and PCOS

The diagnostic criteria for PCOS followed in most of the studies are in accordance with Rotterdam PCOS consensus 2003 (BCJM. Fauser, 2003). Insulin resistance affects 70% of PCOS women, while 10% have diabetes mellitus (DM) (R. Freeman, et al. 2010; K. Farrell, et al. 2010; F. Ovalle, et al. 2002). Over three years, 25% of PCOS women with normal glucose metabolism can become those with abnormal glucose metabolism (MH. Pesant, et al. 2011). Therefore, glucose level alone has lack of sensitivity to predict metabolic disorders in patients with PCOS. In turn, the assessment of insulin resistance is important to evaluate the metabolic conditions in women with PCOS.

Obese women with PCOS are seen more insulin resistant, hyperandrogenic and hypertriglyceridemic although insulin and metabolic indices tend to be similar in lean type of women with PCOS and those without PCOS (P. Acien, et al. 1999). Reproductive disorders in patients with PCOS may manifest insulin resistance. Irregularity of menstrual cycle has been correlated with insulin resistance (T. Strowitzki, et al. 2010). It is reported that hyperinsulinemia in PCOS patients with lower pregnancy implantation rate may be reflected in the local endometrial level due to impairment of insulin receptor action (R. Fornes, et al. 2010). Also, high concentration of insulin in follicular fluid might lead to low pregnancy outcomes in patients with PCOS after in vitro fertilization (S. Takikawa, et al. 2010). Although many areas of PCOS have not been fully understood yet, insulin resistance / hyperinsulinemia plays an important role of pathogenesis and pathophysiology in PCOS.

3. Assessment of Insulin resistance / hyperinsulinemia

In order to assess insulin resistance / hyperinsulinemia, the relationship between insulin sensitivity and insulin secretion is needed to be understood despite their complicated interaction (C. Cobeli, et al. 2007). In general, up-regulation of insulin secretion corresponds to the reduction in insulin sensitivity for healthy subjects with normal glucose tolerance (K. Færch, et al. 2010). Thus, insulin sensitivity and insulin secretion are inversely related to each other and can be seen in a hyperbolic manner. These two variables constantly appear in human with the same levels of glucose tolerance, known as the disposition index (K. Faerch, et al. 2010). The assessment of the disposition index can be calculated from the measurement of insulin sensitivity and insulin secretion by the euglycaemic-hyperinsulinemic clamp technique in combination with the intravenous glucose tolerance test (MA. Adbul-Ghani, et al. 2006a; K. Færch, et al. 2008; M. Laakso et al. 2008). Additionally, a hepatic insulin resistance can be estimated the following multiplication:

1 / (endogenous glucose production x basal insulin concentration)
(C. Brøns et al. 2009; AC. Alibegovic et al. 2009).

A low disposition index indicates the increase in insulin secretion meaning the dysfunction of islet beta-cells; then, resulting in an inadequate hyperinsulinemia (B. Ahre´n, et al. 2002).

There is no concrete measurement of insulin resistance universally. However, various types of methods to measure insulin resistance are proposed, such as hyperinsulinemic euglycernic clamp techniques, fasting methods and 75 g of glucose tolerance test (GTT). In our studies, hyperinsulinemic euglycernic clamp techniques are not utilized because it requires intravenous infusions, extensive time and significant financial resources. With combination of fasting methods and 75g of GTT, insulin resistance and hyperinsulinemia are assessed in our studies. As an index of insulin resistance, the homeostasis model assessment ratio (HOMA-R) is calculated by the formula:

HOMA-R = Fasting insulin level (µU/ml) x
Fasting glucose levels (mg/dl) / 405
(DR. Mattews, et al. 1985).

As a result of the assessment for insulin resistance, HOMA-R with greater than 1.6 is determined to be insulin resistance (H. Tanaka, et al. 2005). In addition, the amount of insulin level with greater than 100 µU/ml at any minutes, or 65 µU/ml at 120 minutes is determined to be hyperinsulinemia. HOMA- β estimates steady state of pancreatic β-cell function by the measurement of fasting plasma glucose and insulin concentrations. It is strongly correlated with high concentration of glycemia as a determinant of its degree. The formula is as follows:

HOMA- β (%) = Fasting plasma insulin (μ U/ml) x 360 /
(Fasting plasma glucose (mmol/L) - 63)
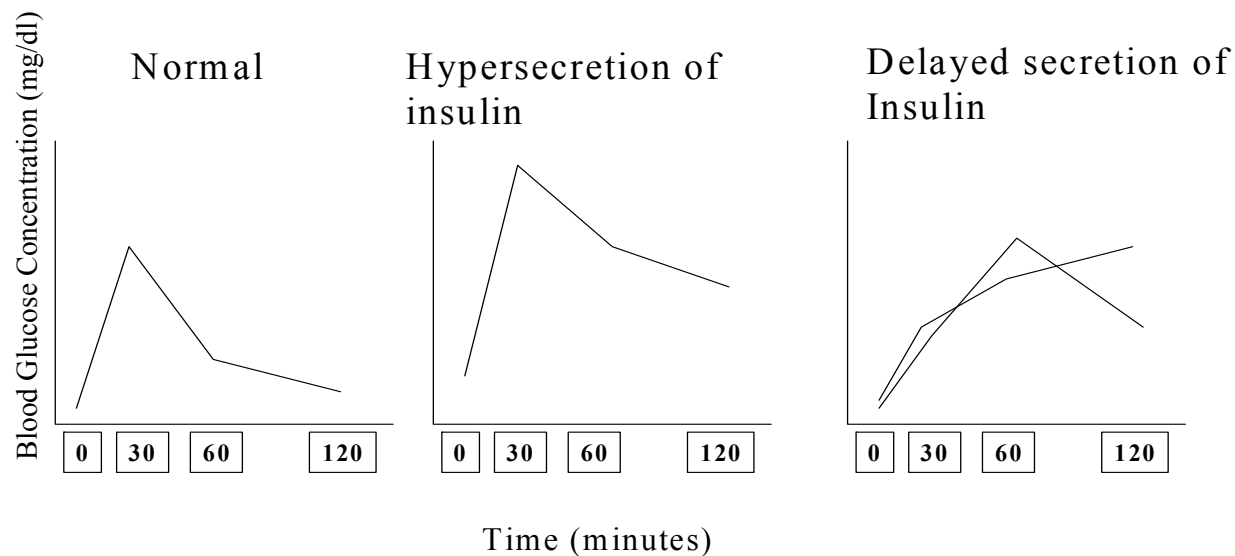(DR. Mattews, et al. 1985).

Fig. 1. Assessment of insulin secretion after GTT, showing blood glucose concentration (mg/dl) on Y axes and time (minutes) on X axes.

Therefore, HOMA- β is effective for understanding progressive type 2 DM. Because almost all of the subjects in our study show normal range of glucose levels, HOMA- β is not analyzed.

Seventy-five grams of glucose is used for the patients in GTT and blood samples are collected at 0, 30, 60 and 120 minutes for circulating blood sugar and insulin levels. As shown in Fig. 1, three types of insulin secretions are indicated. In normal type, highest peak of insulin is secreted at 30 min. and gradually decreased. In hypersecretion type, the insulin level indicates high response at any points – i.e. 0, 30, 60, 120 min. compared with normal. In delayed type, the insulin level gradually increases and/or does not return to normal level at 120 min. Both hypersecretion and delayed secretion indicate insulin abnormalities.

4. Insulin resistance / hyperinsulinemia and lifestyle intervention

Lifestyle management may contribute to the improvement of metabolic complication in overweight and obese women with PCOS. It also correlates with reproductive function for triggering ovulation and maintaining pregnancy by modifying lifestyle as necessary (LJ. Moran, et al. 2009). Control in weight for health benefit, instead of weight-loss purpose only, helps all women with PCOS and it improves psychological distress, hyperandrogenemia and menstrual disturbances that are associated with great food cravings (SS. Lim, et al. 2009). In fact, approximately 5 to 10% of weight loss is enough to ameliorate psychological distress, ovulatory dysfunction, and metabolic disorders (C. Galletly, et al. 1996). Modifying both moderate physical activity and dietary management might also support PCOS women to result in clinical benefit. Simple cardio exercises, such as walking for at least 30 min. per day, are beneficial for PCOS women (ET. Poehlman, et al. 2000).

Although there is still more research needed to conclude the advantageous dietary approach for PCOS women, dietary management may be helpful for improving their reproductive and metabolic functions if the strategies are nutritionally balanced and sustainable for them (LJ. Moran, et al. 2009).

From the above-mentioned point of views, the improvement of lifestyle management and its disciplinary approach that encourages PCOS patients to have good physical activities and dietary strategies may be strongly supportive with targeted medical treatment. In other words, medical treatment and lifestyle therapy should be provided in parallel.

5. Insulin resistance / hyperinsulinemia and ovulatory disorders

The presence of hyperandrogenism in lean and obese women with PCOS is strongly correlated with hyperinsulinemia (RJ. Chang, et al. 1983; A. Dunaif, et al. 1987; A. Dunaif, et al. 1989; A. Dunaif, et al. 1992). The hyperandrogenism results from both increased adrenal and ovarian androgen production (DA. Ehrmann, et al. 1995; RL. Rosenfield, et al. 1990; E. Carmina, et al. 1992; DA. Ehrmann, et al. 1992). Insulin acts via its receptor and appears to contribute ovarian and adrenal androgen biosynthesis (RL. Barbieri, et al. 1986; RL. Barbien, et al. 1988), which amplifies luteinizing hormone induced androgen production by the theca cells and results in hyperandrogenemia (R. Nahum, et al. 1995; DS. Willis, et al. 1998). To improve hyperinsulinemia is effective for circulating androgens to decline to normal level (RD. Murray, et al. 2000). In addition, the upregulation of insuin-like grouth factor- I (IGF-I) receptors may be caused from hyperinsulinemia. IGF-I receptors have the potential to

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stimulate LH-induced androgen synthesis and suppress IGF-binding protein I (IGF-BPI) production by liver (AM. Suikkan, et al. 1988; AM. Suikkan, 1989). Hepatic sex hormone binding globulin (SHBG) production may be inhibited by insulin (N. Botwood, et al. 1995) and it increases the bioactive androgen that eventually causes virilization.

In PCOS, many small antral follicles are characteristically recognized by ultra sonography. These small antral follicles are due to the arrest of growth after reaching a diameter of 5 to 8mm. The arrest of small follicles may be caused by premature activation of LH-mediated terminal differentiation of granulosa cells (S. Franks, et al. 1996). In the normal menstrual cycle, granulosa cells of the dominant follicle become responsive to LH in mid-follicular phase at a follicular diameter of 10mm (SG. Hillier 1994). On the other hand, granulose cells from follicles as small as 4mm in diameter of anovulatory PCOS are responsive to LH. This response to LH is remarkably amplified by insulin. The premature activation of granulosa cells to LH induces terminal differentiation, resulting in the arrest of follicle growth (S. Franks, et al. 1999).

In PCOS patients with ovulatory disorders, insulin resistance, hyperinsulinemia, BMI and visceral fat are studied. As shown in Table 1, values of BMI, HOMA-R and visceral fat accumulation result to be various. However, the results of GTT show abnormal pattern of insulin secretion in most of the cases with PCOS. The effects of treatment with insulin sensitizing agents are present. If ovulation induction with metformin or pioglitazone is failed during one to two cycles, clomiphen citrate is utilized along with one of the insulin sensitizing agents. In PCOS, ten out of 11 cases result in ovulation by treating with insulin sensitizing agents: 5 cases with metformin and 5 cases with pioglitazone. Based on the assessment of GTT including insulin secretion levels, insulin-sensitizing agents are effective for treatment of ovulation induction.

case	BMI	HOMA	obesity with visceral fat	GTT/ insulin secretion pattern	treatment			ovulation
1	19.4	0.68	none	normal	P	+	CC	positive
2	20.8	1.69	none	delayed	P	+	CC	positive
3	23.7	0.65	none	delayed	P	+	CC	positive
4	24.8	2.12	none	delayed	P	+	CC	positive
5	25.6	1.50	none	normal	P			positive
6	25.8	1.42	none	delayed	M			positive
7	27.3	4.04	present	hypersecrestion	M	+	CC	negative
8	27.6	1.45	present	diabetes	M			positive
9	27.8	2.50	present	hypersecrestion	M	+	CC	positive
10	28.0	4.00	none	hypersecrestion	M			positive
11	32.0	3.43	none	hypersecrestion	M			positive

* P = Pioglitazone
M = Metformin
CC= Clomiphene Citrate

Table 1. BMI, HOMA, obesity with visceral fat, insulin secretion after GTT in 11 cases with PCOS, and ovulation results by the treatment of insulin sensitizing agents

6. Insulin resistance / hyperinsulinemia and insulin sensitizing agents in PCOS

As shown in Table 2, insulin-sensitizing agents, metformin and pioglitazone, are most effective on ovulatory disorder in PCOS with insulin resistance and abnormal insulin secretion. It is well known that the functional mechanisms are different in both of the agents. Metformin is an oral biguanide, category B drug for pregnant women, which has been approved for treatment of type 2 diabetes mellitus. It is thought to affect multiple metabolic pathways, decreasing glucose absorption and suppressing hepatic glucose output and gluconeogenesis (F. Mcyer, et al. 1967; N. Wollen, et al 1988). Also metformin directly inhibits androgen production in human thecal cells (GR. Attia, et al. 2001). Side effects are rare, and gastrointestinal disturbances, such as abdominal pain and nausea, rarely cause discontinuation of treatment.

On the other hand, pioglitazone is a thiazolidinedione derivative to be used for treatment of type 2 diabetes mellitus. It is more potent in glucose-lowering effect and favorable effects on abdominal lipid levels including the decrease in circulating triglyceride and free fatty acid levels. Pioglitazone may affect and differentiate on adipocytes via peroxisome proliferator-activated receptorγ (PPARγ). As a result, differentiated adipocytes regulate insulin sensitivity and improve insulin resistance (T Yamauchi, et al. 2001). Side effects are reported as hepatic disturbance and edema but these side effects are tolerable. The main adverse effects reported with pioglitazone are those common to the TZD class: weight gain, pedal edema, bone loss and precipitation of congestive heart failure in at-risk individuals, without any increase in cardiovascular diseases /all-cause mortality. Overall, the safety profile of pioglitazone is favorable and remains a useful option for the treatment of insulin resistant patients (P. Shah, S Mudallar. 2010).

For choice of using insulin-sensitizing agents, High Molecular Weight (HMW) adiponectin is secreted from adipocytes and acts on increasing insulin sensitivity in target organs (T. Kadowaki, et al. 2005). HMW adiponectin is measured in sixty nine cases with non-PCOS and we determine normal range to be over 3.5μg/ml. Ovulation induction in PCOS is performed based on the property of metformin, pioglitazone and levels of adiponectin. In anovulatory PCOS subjects, GTT is first carried out. For positive insulin resistance (IR) with obesity, metformin (500~750mg) is chosen. When HMW adiponectin levels are in normal range for non-obese patients tested positive for IR, a 500mg dose of metformin is chosen, while a 7.5-15mg dose of Pioglitazone is chosen for those with low levels of HMW. For individuals with negative IR, HMW is measured so as to appropriately select either metformin or pioglitazone. Subjects with negative IR have to be abnormal in secretion patterns of insulin and / or glucose metabolic pattern by GTT. For the same subjects with normal levels of HMW adiponectin, metformin (250mg) is used while pioglitazone (7.5mg) is selected for low levels of HMW adiponectin. If ovulation induction with metformin or pioglitazone is failed during three to four cycles, clomiphen citrate is utilized along with one of the insulin sensitizing agents. It is also significant that improving life-style such as daily exercise and diet is highly recommended along with treatment using insulin sensitizing agents.

Ovulation induction in PCOS subjects is applied to 38 cases shown in Table 2. Ovulation rate is very high, 97.3 % (37/38). High pregnancy rate is also observed, 73.0% (27/37). Rate of combination use with clomiphen citrate is 36.8% (14/38). Therefore, the proposed management protocol satisfies treatment of patients with anovulatory PCOS.

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Ovulation rate:	97.3% (37 / 38)	
Pregnancy rate:	73.0% (27 / 37)	
Abortion rate:	11.1% (3 / 27)	
Pregnancy rate with metformin:		69.2% (18 / 26)
Pregnancy rate with pioglitazone:		81.8% (9 / 11)
Rate of combination use with clomiphene citrate:		38.8% (14 / 38)

Table 2. Results of ovulation induction in PCOS subjects based on the properties of insulin sensitizing agents and levels of high molecular weight adiponectin.

7. Insulin resistance / hyperinsulinemia and implantation disorder

To study how insulin resistance / hyperinsulinemia affects implantation, GTT is carried out in seventy-eight subjects who failed implantation by the treatment of freeze-thawing embryo transfer method. Although embryos with good quality are transferred at least more than one time, pregnancy is not achieved. In this study, good quality embryos are defined as over four cells and less than 30% of fragmentation. Thirty five out of 78 cases reveal insulin resistance and / or hyperinsulinemia by GTT. Then, 11 out of 35 cases have PCOS. After treated with metformin, twenty out of 35 cases become pregnant by freeze-thawing embryo transfer. Six cases with PCOS become pregnant; five cases delivered and 1 case aborted. The results of this treatment are summarized in Table 3. The result indicates the possible ground implantation mechanisms.

Insulin resistance / hyperinsulinemia		35	cases
	(PCOS case)	(11	cases)
Pregnancy after treatment		20	cases
	(PCOS case)	(16	cases)
Delivered		16	cases
	(PCOS case)	(5	cases)
Aborted		4	cases
	(PCOS case)	(1	case)

Table 3. Results of implantation outcomes by freeze-thawing embryo transfer after treatment by insulin sensitizing agent (metformin).

According to Jakubowicz et al., glycodelin, insulin-like-growth factor-binding protein 1 (IGF-BP1), uterine vascularity and blood flow are studied for association with treatment of metformin and placebo in PCOS (DJ. Jakubowicz, et al. 2001). Glycodelin is a protein synthesized by secretary / decidualized endometrial glands. Circulating glycodelin may reflect endometrial function such as endometrial maturation and inhibition of endometrial immune response to the embryo (M. Seppala, et al. 1988; M. Julkunen, et al. 1990; AE. Bolton, et al. 1987; M. Julkunen, 1986; N. Okamoto, et al. 1991). IGF-BP1 is a protein that appears to facilitate adhesion process at the feto-maternal interface and may play an important role in the periimplantation period (LC. Giudice, et al. 1998; JI. Jones, et al. 1993). In comparison with placebo, metformin treatment increases concentration of glycodelin and

IGF-BP1 in luteal phase up to 3 to 4-fold. Besides, it increases in vascular penetration and increase in blood flow of spiral arteries that is demonstrated by 20% reduction in the resistance index. From this, endometrial function and amelioration of its environment may be improved by treatment of hyperinsulinemia, which has a strong correlation with insulin resistance and PCOS.

8. Insulin resistance / hyperinsulinemia and early pregnancy loss

Women with PCOS are associated with 30 – 50% of early pregnancy loss at a higher risk than normal women (L. Regan, et al. 1990; HR. Gray, et al. 2000). They are also involved in 36 – 82% of the risk for recurrent early pregnancy loss (HS. Liddell, et al. 1997). Treatment of insulin sensitizing agents is applied to 38 cases with PCOS that resulted in ovulation of 37 cases. As shown in Table 3, twenty seven cases became pregnant after the treatment. Then, the abortion rate is 11.1% (three out of 27 cases) that is almost as low as that of normal women. This explains treatment of insulin sensitizing agents might be effective for sustaining early pregnancy periods. This concept can be also emphasized (DJ. Jackbowicz, et al. 2002), the rate of early pregnancy loss is 8.8% as compared with 41.9% for control group in PCOS. Metformin therapy during pregnancy in women with PCOS is safely associated with reduction of spontaneous abortion for the first trimester and is not teratogenic without adverse effects on biological and physical conditions of baby. In addition, metformin therapy improves the insulin level, HOMA- R and high plasminogen activator inhibitor activity (PAI-Fx) (CJ. Glueck, et al. 2002). Therefore, metformin therapy that has insulin-lowering effect might be accountable for protecting early pregnancy loss. Nevertheless, sustaining the pregnancy might be achieved through lifestyle intervention.

9. Conclusion

PCOS is a very common complex that occurs in approximately up to 20% of women of reproductive age and threatens fertility and metabolic condition as well. And also, it is chronic diseases, such as dyslipidemia, type 2 diabetes and cardiovascular diseases, across the lifespan. These conditions represent a major health and financial burden. It is mentioned that PCOS is the beginning of lifestyle-related diseases. Although it is still challenging to fully comprehend and reveal this unknown syndrome for researchers, PCOS has been known to be involved in insulin resistance / hyperinsulinemia. It is well-known that insulin resistance / hyperinsulinemia is affected by lifestyle factors, such as diet and physical activities. As mentioned above, approximately 5 to 10% of weight loss is enough to ameliorate ovulatory dysfunction and metabolic disorders. Therefore, the improvement of lifestyle is a key to overcoming reproductive and metabolic disorders in women with PCOS. Also, the efficacy of insulin sensitizing agents may contribute to the amelioration of insulin resistance / hyperinsulinemia and be also effective for the reproductive and metabolic functions of PCOS women. Insulin sensitizing agents consequently facilitate ovulation, implantation and maintenance of pregnancy. As reiterated, both lifestyle management and appropriate medication might be conductive to the improvement of adverse effects for reproductive processes by insulin resistance / hyperinsulinemia in PCOS (S. Franks. 2011; T. Sakumoto, et al. 2010). Nevertheless, it requires further study for comprehension of PCOS. More understanding of the complexity of PCOS might lead to optimal management of PCOS for clinicians and patients.

The relationship between differentiation of visceral adipocytes and reproductive processes is shown in Fig 2 (T. Yamauchi, et al. 2001; T. Sakumoto, et al. 2010).
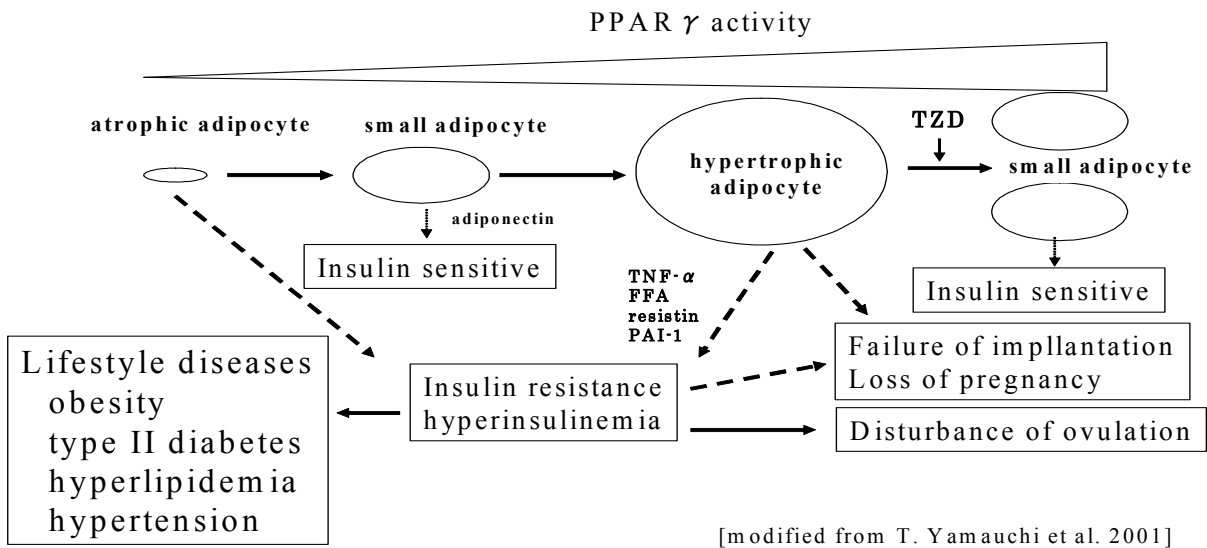
FFA : free fatty acid, PAI-1 : plasminogen activator inhibitor 1,
PPAR-γ: peroxisome proliferator-activated receptor gamma
TNF-α: tumor necrosis factor alpha, TZD: thiazolidinedione

Fig. 2. The relationship between differentiation of visceral adipocytes and reproductive processes (T. Sakumoto, et al. 2010)

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11. References

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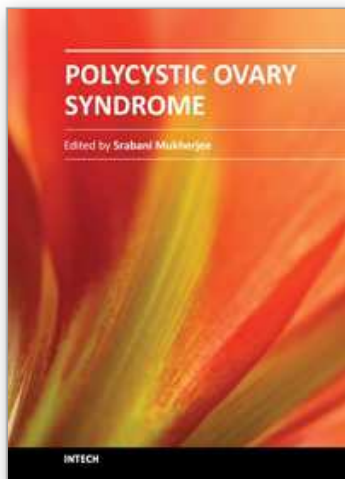
Polycystic Ovary Syndrome

Edited by Dr. Srabani Mukherjee

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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