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## The role of adiponectin in reproduction: from polycystic ovary syndrome to assisted reproduction

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### Abstract

**Objective**—To summarize the effects of the adipokine adiponectin on the reproductive endocrine system, from the hypothalamic-pituitary axis to the gonads and target tissues of the reproductive system.

**Design**—A Medline computer search was performed to identify relevant articles.

**Setting**—Research institution.

**Intervention(s)**—None.

**Result(s)**—Adiponectin is a hormone secreted by adipose tissue that acts to reduce insulin resistance and atherogenic damage, but it also exerts actions in other tissues. Adiponectin mediates its actions in the periphery mainly via two receptors, AdipoR1 and AdipoR2. Adiponectin receptors are present in many reproductive tissues, including the central nervous system, ovaries, oviduct, endometrium, and testes. Adiponectin influences gonadotropin release, normal pregnancy, and assisted reproduction outcomes.

**Conclusion(s)**—Adiponectin, a beneficial adipokine, represents a major link between obesity and reproduction. Higher levels of adiponectin are associated with improved menstrual function and better outcomes in assisted reproductive cycles.

### Keywords

Adiponectin; hypothalamus; pituitary; gonads; reproduction; polycystic ovary syndrome; PCOS; pregnancy; embryo development; assisted reproduction

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Obesity has reached epidemic proportions in developing and developed countries. According to the practice committee of the American Society for Reproductive Medicine, obesity is the most common chronic disease in the U.S. (1). Despite worldwide awareness and international campaigns, the incidence of obesity is increasing, and obesity has been described as the new worldwide epidemic (2). In 2009, the American Obesity Association reported that obesity affects nearly one-third of the adult American population, ~60 million individuals. Today, 64.5% of adult Americans (~127 million) are categorized as being overweight or obese. Each year, obesity causes at least 300,000 excess deaths in the U.S., and health care costs of American adults with obesity amount to ~\$100 billion.

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An understanding of adipose tissue and its functions is therefore of special interest to identify mechanisms that account for the metabolic consequences of obesity. Among the main endocrine products of the adipose tissue are the proteins leptin, adiponectin, and resistin. Leptin, first described over a decade ago (3), has been thoroughly studied regarding reproduction and at several levels of the reproductive axis, from the pituitary to end organs (4–6). In contrast, few reports have summarized the effects of adiponectin on the reproductive organs, either at a molecular level or for clinical relevance. The present review focuses on the role of adiponectin as a hormone in order to clarify its role in reproduction.

## ADIPOSE TISSUE

To meet metabolic demands and needs of energy expenditure, adipose tissue secretes several proteins and bioactive peptides—adipokines—(Table 1) that act either locally (paracrine or autocrine action) or systemically (endocrine action) (7). Adipose tissue is considered to be a true endocrine gland (8). Many of these molecules directly or indirectly influence metabolism, cardiovascular function, immunity or reproduction (Fig. 1). An excellent example of the importance of adipose tissue in reproduction is its ability to convert androgens to estrogens, owing to the presence of P450 aromatase in adipose tissue.

Adipose tissue is primarily composed of lipid-laden adipocytes surrounded by loose connective tissue. In humans, most fat is white adipose tissue, in contrast to animals, which have brown adipose tissue (9). The abundant adipocytes serve as triglyceride storage (9) and are surrounded by a network of collagen fibers, vascular elements, fibroblasts, and immune system cells. The metabolic role of adipose tissue is as an energy storage compartment. In cases of prolonged fasting, lipolysis of adipose tissue promotes fatty acid delivery to be used by muscle, liver, and kidneys. Conversely, a glucose load stimulates lipogenesis through insulin (9), and thus adipose tissue maintains energy homeostasis. Many of the metabolic consequences of obesity are caused by altered secretion of adipokines.

## ADIPONECTIN

### Structure and Expression

Adiponectin is a member of the adipose-secreted proteins called adipocytokines (Fig. 2). Adiponectin was first described in 1995 as adipocyte complement-related protein of 30 kDa (Acrp30) (10). Adiponectin was discovered independently by several laboratories, thus its various names: Acrp30, adipose most abundant gene transcript 1 (apM1), adipose-specific gene adipoQ (AdipoQ), and gelatin-binding protein of 28 kDa (GBP28). Adiponectin is a 244-amino acid protein (molecular weight 30,000 Da) derived exclusively from adipocytes in white adipose tissue (6). Adiponectin is the protein product of the *APM1* gene transcript, which is located at chromosome 3q27, close to the locus responsible for type II diabetes and adiposity (11, 12).

Of note, adiponectin is one of the most abundantly secreted adipokines and corresponds to 0.05% of the serum proteins (13). In fact, serum levels are 3–30  $\mu\text{g/mL}$  in humans and 3–6  $\mu\text{g/mL}$  in rodents (14). Adiponectin is related to the complement 1q family and contains a carboxyl-terminal globular domain and an amino-terminal collagenous domain. Adiponectin is secreted by adipose tissue (Fig. 3) in the form of a trimer as a low-molecular-weight (LMW), a combination of two trimers as a middle-molecular-weight (MMW), or as six trimers as a high-molecular-weight (HMW) form (15) and circulates either as a trimer or an oligomer (16–18). Adiponectin is post-translationally modified by hydroxylation and glycosylation, and circulating levels in mammals have been shown to be differentially glycosylated, with approximate molecular weights of >250,000, 180,000, and 90,000 Da, which correspond to HMW, MMW, and LMW forms of adiponectin (18). Similarly to

leptin, adiponectin levels are lower in men (19, 20), obese individuals, individuals with diabetes, and those with coronary artery disease (14, 21, 22). Adiponectin mediates its action in the periphery principally through two receptors, AdipoR1 and AdipoR2 (23), although a third receptor, t-cadherin, has also been identified (24).

AdipoR1 and AdipoR2 receptors are 7-transmembrane receptors that belong to a recently discovered family of 11 progestin AdipoQ receptors (PAQRs), but they are structurally and functionally distinct from G-protein-coupled receptors (25). AdipoR1 and AdipoR2 are also known as PAQR1 and PAQR2, respectively. Both AdipoR1 and AdipoR2 bind adiponectin with an  $EC_{50}$  in the range of 0.7–2.4 pmol/L (26). Related PAQR family members PAQR5 (also known as membrane progesterone receptor gamma [mPR $\gamma$ ]), PAQR 7 (mPR $\alpha$ ), and PAQR8 (mPR $\beta$ ) exhibit strong binding to progesterone ( $EC_{50}$  1–3 nmol/L in yeast), show a similar pattern of activation to known membrane-associated progestin effects, and transduce progestin-dependent signals (26). For example, PAQR5, PAQR7, and PAQR8 are activated by 17 $\alpha$ -hydroxyprogesterone, an agonist that is known to activate membrane progesterone, but not the nuclear progesterone receptor. Thus, PAQR receptors closely related to AdipoR1 and AdipoR2 (25, 26) may have an important role in reproduction, although incontrovertible evidence for the *in vivo* role of PAQR5, PAQR7, and PAQR8 in progesterone action would require targeted deletion in mice or a similar approach.

Adiponectin functions as an agonist of PAQR3, a previously incompletely characterized member of the newly discovered PAQRs. Therefore, PAQR3 could potentially be a newly discovered target receptor of adiponectin in the PAQR family. AdipoR1 receptor is expressed mainly in skeletal muscle, activates the adenosine monophosphate-activated protein kinase (AMPK) pathway, and shows a high affinity to globular adiponectin and low affinity for full-length adiponectin (Fig. 3). In contrast, AdipoR2 receptor is enriched in liver and acts through peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) pathway. Both AdipoR1 and AdipoR2 show affinity for both molecular forms of adiponectin. Although studies have failed to demonstrate a blood-brain transport of adiponectin, both AdipoR1 and AdipoR2 are widely distributed in the brain (see below).

Actions of adiponectin are mediated through activation of AMPK, leading to inhibition of acetyl coenzyme A carboxylase and an increased fatty acid beta-oxidation (27). Activation of AMPK acts to regulate energy homeostasis of the cell via fatty acid oxidation and glucose uptake stimulation. Adiponectin is markedly reduced in obesity and rises with prolonged fasting and severe weight reduction.

Adiponectin functions as an insulin-sensitizing agent by reducing hepatic glucose production and enhancing insulin action in the liver (28, 29). Studies have shown that adiponectin lowers levels of glucose, free fatty acids, and triglycerides *in vivo* (30–32) and increases fatty acid oxidation in the liver via a reduction in CD36 expression, thus reducing fatty acid influx and liver triglycerides (33). Adiponectin levels negatively correlate with levels of fasting insulin, glucose, and triglyceride (21), and the administration of insulin sensitizers significantly increase serum adiponectin levels in insulin-resistant humans (34). Adiponectin, particularly HMW adiponectin, is increased by thiazolidinediones (TZDs) and mediates the insulin-sensitizing effect of this class of antidiabetic drug (35). Adiponectin levels are low in insulin-resistant states and increase in insulin-sensitive states, such as with weight loss or treatment with thiazolidinediones (21). Further evidence for a key role for adiponectin in glucose homeostasis is the hepatic insulin resistance found in rodents and humans lacking adiponectin. It is important to mention that *in vivo* studies in humans are associative and that more direct evidence for the importance of adiponectin is provided by experiments in animals. In contrast, adiponectin treatment enhances insulin sensitivity, primarily by suppressing glucose production. High adiponectin levels may protect the

cardiovascular system and reduce the incidence of myocardial infarction (36, 37) while accelerating endothelial renewal (38).

In addition to its effects on insulin sensitivity, adiponectin increases lipoprotein lipase and lowers lipid levels (39, 40), increases nitric oxide production in endothelial cells and induces angiogenesis (41), and mediates antiinflammatory (42) and anti-atherogenic actions (43). It was recently reported that adiponectin levels were low in patients with breast cancer (44), endometrial cancer (45), gastrointestinal cancer (46, 47), and prostate cancer (48). Therefore, adiponectin acts as a hormone to fine-tune energy homeostasis involving food intake and the catabolism of carbohydrate and lipid (49) and may offer an interesting alternative treatment for type II diabetes, obesity, and metabolic disturbances (2).

### Adiponectin in the Hypothalamus and Pituitary

Both AdipoR1 and AdipoR2 are expressed in human pituitary (Table 2), suggesting local modulation of the central reproductive endocrine axis by adiponectin (50). Although earlier studies (51) reported that adiponectin did not cross the blood-brain barrier, subsequent studies (50) showed that AdipoR1 was expressed in the hypothalamus and nucleus basalis of Meynert. In 2008, Wen et al. (52) reported that both adiponectin receptors were expressed in arcuate and lateral hypothalamic nuclei. Moreover, the expression and regulation of multiple adipose-related hormones (including adiponectin) in the central nervous system and pituitary gland was described (53).

Adiponectin has also been shown to regulate hormone secretion and gene expression in two critical endocrine cell types of the pituitary involved in reproduction: somatotrophs and gonadotrophs. Adiponectin inhibited LH and GH release as well as both ghrelin-induced GH release and GnRH-stimulated LH secretion in short-term (4 h) GT1–7 cells derived from GnRH neurons. Adiponectin inhibited GnRH secretion via activation of AMPK (52). These results were supported by Lu et al. (54), who reported that adiponectin acutely reduced basal and GnRH-stimulated LH secretion through increased phosphorylation of AMPK but had no impact on FSH levels. At the level of the hypothalamus, adiponectin also influenced oxytocin-secreting neuron excitability, perhaps explaining increased oxytocin secretion in the obese population (55). Furthermore, adiponectin increased GHRH-R and GH secretagogue-R mRNA content, which are the two main stimulatory receptors in somatotrophs (56). Taken together, these results suggest a role for adiponectin as a link between adiposity and reproduction. Specifically, low levels of adiponectin may contribute to chronically elevated LH levels.

### Adiponectin and the Gonadal Organs

**Ovaries**—The effects of adipokines on the process of ovulation and ovarian steroidogenesis have not been extensively studied (57). Although leptin levels have been correlated with progesterone levels throughout the menstrual cycle, Lord et al. (58) were the first to demonstrate that pig ovaries and ovarian follicles expressed AdipoR1 and AdipoR2. Subsequent studies confirmed expression of these receptors in the human ovary (59). The isoforms of adiponectin (trimer, hexamer, and HMW) were present in both porcine and human follicular fluid at concentrations equivalent to serum concentrations (60, 61).

Page et al. (62), as well as Lanfranco et al. (63), showed that increased T levels in humans were inversely correlated with circulating adiponectin levels, and a similar inverse relationship has been observed in mice (64). Ledoux et al. (60) found that *AdipoR1* and *AdipoR2* mRNA was present in theca and granulosa cells, and that adiponectin receptors (AdipoR1, AdipoR2) were detected in human granulosa cells and mediated adiponectin action for increased production of P and E<sub>2</sub> by insulin-like growth factor (IGF) I (65).

Dupont et al. (66) highlighted the expression of PPARs and AMPK (the main adiponectin mediators) in the ovary.

In 2008, Gutman et al. (67) first demonstrated the *in vivo* induction of adiponectin by gonadotropins in the human ovary after treatment with recombinant LH (Table 2). The addition of recombinant LH during the late follicular phase may enhance follicular insulin sensitivity, resulting in reduced androgen levels through a cascade mediated by increased production of adiponectin. Lagaly et al. (68) showed that adiponectin inhibited P- and LH-dependent A production and insulin in theca cells *in vitro*. This was accompanied by reduction of *LHr*, *Cyp11a1*, and *Cyp17a1* transcripts in theca cells; thus adiponectin reduced theca cell steroidogenesis. However, adiponectin did not affect insulin-induced proliferation of theca cells from large follicles or granulosa cell function. In addition, LH was found to increase *AdipoR2* mRNA in theca cells, but not granulosa cells (68). Thus, adiponectin can directly induce gene expression in theca cells, which has potential relevance to the pathophysiology of polycystic ovary syndrome (PCOS; see below). The synergistic role of adiponectin with insulin or IGF-I is consistent with the insulin-sensitizing role of adiponectin.

**Anovulation (PCOS)**—Polycystic ovary syndrome is characterized by the presence of clinical or biochemical hyperandrogenism, chronic anovulation, and polycystic ovaries (69) and is frequently associated with insulin resistance. Obesity and insulin resistance are accompanied by a decrease in SHBG and an increase in the free androgen index (70). Considering the insulin-sensitizing actions (71–74) of adiponectin, its lower levels in obesity (75), and the fact that adiponectin levels were reduced by T (76), it is reasonable to postulate that adiponectin levels would be low in women with PCOS. Several studies have addressed this point (Table 3). Some studies (77, 78) observed no difference in adiponectin levels between PCOS women and normal weight-matched control subjects, whereas other studies showed lower adiponectin levels in PCOS women (79, 80). Meta-analyses of these studies, in combination with the homeostasis model assessment of insulin resistance (HOMA-IR), supported the conclusion that adiponectin levels were lower in women with PCOS (81). According to one meta-analysis (81), adiponectin levels were lower in PCOS women compared with healthy control subjects of a similar body mass index (BMI). Furthermore, adiponectin levels were lower in obese PCOS women compared with non-PCOS obese women. Adiponectin levels were related to insulin sensitivity: The more insulin-resistant patients had lower adiponectin levels (81). As mentioned above, it is possible that lower levels of adiponectin may contribute to the increased levels of LH observed in some women with PCOS.

In women without PCOS, adiponectin has been negatively correlated to T (76). In women with PCOS, adiponectin levels were also negatively related to T levels (82) and to free androgen index (83), cholesterol, triglycerides, glucose levels, and diastolic blood pressure (82). Because adiponectin levels are related to insulin resistance, low adiponectin levels can not be considered to be characteristic of PCOS. Instead, the alterations relate to the pathophysiology of insulin resistance, and for this reason measurement of adiponectin in a patient with PCOS is not indicated. Insulin and glucose levels—which are often measured in PCOS—in combination with BMI correlate as expected with adiponectin levels (81).

**Oviduct**—Though far less studied, adiponectin may play a role in oviductal function. The oviduct has been found to produce soluble factors that influence reproduction and possibly fetal development. The oviductal fluid consists of glycoproteins, protease inhibitors, regulatory molecules, cytokines, growth factors, cytokines, enzyme-binding proteins, and immunoglobulins (84). Arcancho et al. (85) were the first to show that the oviduct of cycling rats produces and secretes leptin and adiponectin (Table 2). Immunoreactivity for both

adipokines was found in the apical region of the secretory epithelial cells, but only in the isthmus and ampulla, and immunostaining was stronger in the isthmus and changed throughout the estrous cycle in the ampulla, increasing from proestrus to estrus. A specific role for the protein in the oviduct remains to be shown.

**Endometrium**—Recent findings suggest a possible role of adiponectin in endometrial function. Both AdipoR1 and AdipoR2 are highly expressed in the pig endometrium (86). In 2006, both receptors were shown to be present in the endometrial and glandular human epithelium and in stromal fibroblasts (87), and transcript levels were higher during the midluteal phase of the cycle. Adiponectin acts through adenosine monophosphate-activated protein kinase phosphorylation in epithelial and stromal endometrial cells. The fact that the expression of both genes was increased in the midluteal phase when the implantation occurs suggests that the homeostatic and antiinflammatory effects of adiponectin in the endometrium might affect implantation. Interestingly, adiponectin levels were lower in women with endometriosis compared with healthy women. In women with endometriosis, adiponectin levels were inversely correlated to endometriosis and adhesion scores (88). Only one study evaluated adiponectin and uterine leiomyomas (89), and the investigators reported that women with leiomyomas had significantly lower adiponectin levels.

**Testes**—Whereas most studies of obesity and infertility focus on the female partner, evidence suggests a significant effect of obesity upon male reproductive function (Table 3). Despite a recent study showing no significant change in sperm parameters relative to BMI (90), oligozoospermia and asthenozoospermia have been found to increase with an increased BMI, worsening from overweight to obese men (91). Based on the role of adiponectin in the ovary, investigators studied the possible expression of adiponectin in the rat testis. Interstitial Leydig cells were found to express adiponectin mRNA, whose levels were marginally regulated by pituitary gonadotropins (92). In addition, expression of transcripts encoding AdipoR1/R2 was detected and ex vivo and recombinant adiponectin inhibited T secretion, whereas it failed to change levels of stem cell factor and antimullerian hormone (92). Furthermore, Ocon-Grove et al. (93) reported expression of AdipoR1/R2 mRNA in chicken testis, adding that sexual maturation was likely associated with an up-regulation in testicular AdipoR1/R2 and consequent influence on steroidogenesis, spermatogenesis, Sertoli cell function, and spermatozoa motility.

### Adiponectin and Assisted Reproduction

Obesity of the female partner is associated with a suboptimal outcome during an assisted reproduction procedure. Although most studies consider obesity as a negative predictive factor, others report differences only when marked obesity (BMI >35) is encountered. Nevertheless, the majority of studies support the conclusion that obesity predicts reduced success at ART (94). To date, few investigators have tested the correlation of adiponectin levels with ART outcomes.

Based on the fact that adiponectin is reduced by increasing concentrations of estrogens and increased by hCG, Liu et al. (95) studied whether adiponectin levels were altered in women undergoing assisted reproduction. In that study, the investigators followed 52 women during an IVF cycle and found a decrease in adiponectin levels from day 0 (baseline) to the day of hCG injection. This decrease was partly explained by high E<sub>2</sub> levels, though the E<sub>2</sub> levels on day of hCG injection were not correlated with adiponectin levels. On the contrary, post-hCG adiponectin levels showed a subsequent increase, which in turn correlated with increased levels of P after transfer, possibly explained by lipid accumulation and subsequent P production due to adiponectin (95). Consistent with these observations, adiponectin levels were found to be higher in 9 out of 32 women participating in IVF-ICSI who became

pregnant, compared with lower circulating levels in unsuccessful cycles. Levels of adiponectin were higher among the group with successful pregnancy on the day of oocyte retrieval as well as the preceding 3 days. Interestingly, adiponectin levels were higher in the group with successful outcome, despite no difference at the beginning of ovarian stimulation (96). Moreover, in the same study, adiponectin was present in the follicular fluid, but levels were not correlated with fertilization rates or the gonadotropin dosage. The authors speculated that because follicular fluid adiponectin levels differed at various stages of blastomere development, levels of adiponectin might hold predictive value (96). A second case-control study of 56 women found that adiponectin levels on the day before gonadotropin administration correlated with the number of oocytes retrieved and that adiponectin levels were higher in women who conceived (97).

Independently of the number of oocytes obtained or estrogen levels, adiponectin levels in the follicular fluid were found to be higher in women that received recombinant LH, possibly relating to lower androgen and increased insulin sensitivity (67). In addition to the correlations observed in vivo, adiponectin receptors were found to be present in human granulosa cells, promoting an increase in P and E<sub>2</sub> locally in granulosa cells (65), and AdipoR1 and AdipoR2 were found to be regulated by hCG treatment in rats (98). The mechanism responsible for the improved pregnancy outcome might be enhanced development of oocytes (observed in porcine embryos, possibly through an inhibitory mitogen-activated protein kinase [MAPK] pathway), with a positive effect on the meiotic maturation and a superior rate of embryo development to the blastocyst stage (99).

### Adiponectin in Pregnancy

The fact that adiponectin is implicated in the pathogenesis of insulin-resistant states, and that an increase in adiponectin levels promotes insulin sensitivity, raises the question of whether adiponectin plays a metabolic role in pregnancy. The beginning of pregnancy is characterized by tissue accretion, whereas late pregnancy is notable for insulin resistance and facilitated lipolysis (100). In early pregnancy, insulin secretion increases, although insulin sensitivity is unchanged, decreased, or even increased (100, 101). In late gestation, because of the progressive increase in postprandial glucose, insulin requirements must increase (97).

### Adiponectin and the Placenta

The human placenta was found to express virtually all known cytokines (101). Cytokines are produced by three different placental cell types: the Hofbauer cells, the trophoblast cells, and the vascular endothelium cells (101). Adiponectin receptors are present in the human and rat placenta (102). Both human and rodent placentas express adiponectin (103). Of note, placental cytokine release is positively correlated to adiponectin levels (104). AdipoR2, in particular, is expressed in human syncytiotrophoblast and cytotrophoblast (103). The trophoblast and the placenta are also local sources of adiponectin secretion (102). Placental adiponectin secretion has been demonstrated in vitro, implicating placenta in a complex system of source and target function. Placental adiponectin acts through a pathway common for adiponectin, by altering the phosphorylation status of p38 and MAPK (102).

Studies have also suggested a role for adiponectin in the function of the placenta (Table 3). Obesity is recognized as a risk factor for preeclampsia, and adiponectin levels were lower during the first trimester in women with preeclampsia (105), whereas adiponectin and HMW adiponectin levels were increased in preeclampsia, perhaps a physiologic response to restore insulin sensitivity (106). Placental tissues from women with severe preeclampsia show reduced expression of adiponectin (107). Whether adiponectin has a direct role in this condition as related to obesity (108) or gestational diabetes (109) remains to be confirmed,

but recent data suggest a role for adiponectin and AdipoR1 in placental angiogenesis and placental apoptosis (110).

Recent findings also show that adiponectin secretion and adiponectin transcript levels in white adipose tissues decline as gestation progresses, even in lean women, which suggests that the adiponectin decrease is due to pregnancy-associated factors (111, 112). High E<sub>2</sub> levels in vivo tend to lower adiponectin levels, possibly adding to the decrease observed during pregnancy (113). Although women tend to have higher levels of adiponectin in general, gestational diabetes mellitus (GDM) is associated with reduced serum adiponectin levels both during pregnancy and after delivery. Adiponectin is negatively correlated with HOMA-IR, and a decrease in maternal adiponectin after delivery indicates a significant placental contribution to adiponectin production (114). Moreover, adiponectin levels correlate with whole-body insulin sensitivity (115). This is understandable because of the insulin-sensitizing effects of adiponectin in muscle and liver; adiponectin reduces hepatic glucose production and enhances insulin action in the liver and peripheral utilization of glucose. Given these data regarding expression of AdipoR1/R2 in the placenta, adiponectin may affect the constantly changing metabolic state throughout pregnancy. Studies between women with gestational diabetes mellitus and matched normal control subjects showed an alteration of proinflammatory cytokines in women with GDM; adiponectin levels were reduced in women with GDM, whereas interleukin-beta levels were increased. Moreover, birth weight was negatively correlated with second-trimester adiponectin levels (114).

### Adiponectin and the Fetus

Expanding the link between adiponectin and the placenta, and given the data that relate adiponectin to fat distribution and insulin resistance, raises the question of adiponectin levels in the fetus. Cord adiponectin levels were found to be significantly higher and not related to maternal adiponectin levels, thus demonstrating a fetal source of adiponectin (116). While adiponectin concentrations were found to be relevant only between maternal serum and breast milk (117), low levels of adiponectin in cord serum tended to occur in fetuses disproportionately large for their placental weight and vice versa (118). Long-term follow-up of children with low cord adiponectin levels during fetal life predicted a more pronounced weight gain at in the first 6 months of life, as well as an increased BMI and central adiposity at age 3 (119). Both HMW and LMW adiponectin were detected in fetal plasma and were stained in in vascular endothelial cells of fetal organs, skeletal muscle, kidney, and brain. Moreover, the HMW adiponectin and total adiponectin levels are found to be higher in umbilical plasma than in adult plasma and were associated with lower insulin concentration and possibly lower insulin resistance in umbilical plasma, reflecting higher insulin sensitivity of the fetus compared with the adult (120). Furthermore, although the relationship between intrauterine growth retardation (IUGR) and perinatal and long-term complications is established, attempts to correlate low adiponectin levels with IUGR are inconclusive, because the majority of children resulting from IUGR are not found to have low adiponectin levels (121, 122). Nevertheless, mothers who carried IUGR pregnancies were found to have reduced adiponectin levels, possibly explaining the insulin insensitivity of their offspring in term (123).

## CONCLUSION

Obesity is an epidemic, causing serious health issues, including anovulation and infertility. Because obesity is associated with low adiponectin levels, and given that many reproductive endocrine tissues express adiponectin receptors, adiponectin represents an important hormonal link between adipose tissue and the reproductive system. The relationship between obesity and normal endocrine reproductive function is fertile ground for future research.



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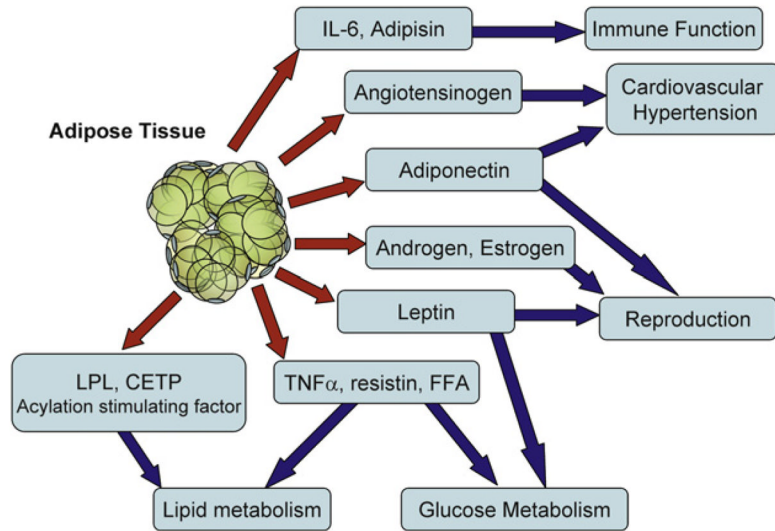
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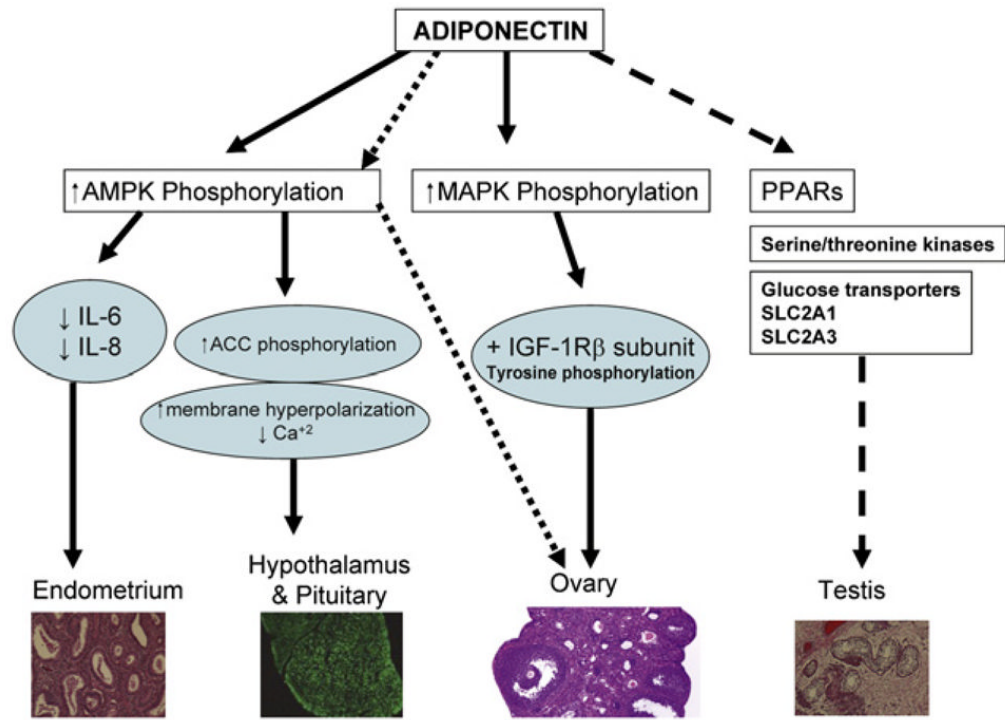
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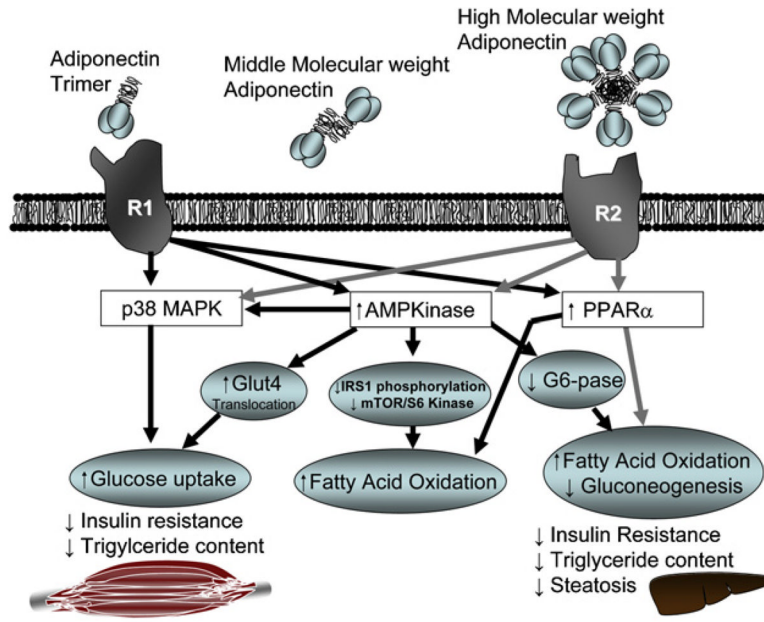
**FIGURE 1.** Adipose tissue functions as an endocrine gland. Adipose tissue secretes proteins and lipids and metabolizes hormones that regulate not only energy homeostasis, but also influence reproduction, immune function, and cardiovascular disease and hypertension. CETP = cholesteryl ester transfer protein; FFA = free fatty acids; IL = interleukin; LPL = lipoprotein lipase; TNF = tumor necrosis factor.





**FIGURE 2.**

Adiponectin acts through the indicated pathways to influence organs involved in male and female reproduction. ACC = acetyl CoA carboxylase; AMPK = adenosine monophosphate-activated protein kinase; IGF = insulin-like growth factor; IL = interleukin; MAPK = mitogen-activated protein kinase; PPAR = peroxisome proliferator-activated receptor. SLC2A1 (GLUT1) = soluble carrier family 2 (facilitated glucose transporter) member 1; SLC2A3 (GLUT3) = soluble carrier family 2 (facilitated glucose transporter) member 3.



**FIGURE 3.** Molecular structure of adiponectin and its receptors AdipoR1 and AdipoR2 and the indicated signaling pathways in muscle, adipose tissue, and liver. Adiponectin occurs in three molecular forms with globular and coiled domains: trimeric (low molecular weight), hexameric (middle molecular weight), or multimeric (high molecular weight). Two trimers associate to form a disulfide-linked hexamer (MMW). The HMW complex consists of 12–18 monomers and is most active in suppressing hepatic glucose production. The trimeric form is most potent for induction of AMPK activation and fatty acid  $\beta$ -oxidation in skeletal muscles. G6-pase = glucose-6-phosphatase; Glut = glucose transporter; IRS = insulin receptor substrate; mTOR= mammalian target of rapamycin; other abbreviations as in Figure 2.

**TABLE 1**

Products of the adipose tissue.

Hormones	Leptin, resistin, adiponectin, estrogens
Cytokines	Interleukin-6, tumor necrosis factor alpha
Extracellular proteins	Fibronectin, laminin, collagen
Enzymes	17 $\beta$ -Hydroxy steroid dehydrogenase (HSD), 11 $\beta$ -HSD 1, p450 aromatase, lipoprotein lipase
Renin-aldosterone system proteins	Renin, angiotensinogen I, angiotensinogen II
Acute-phase proteins	Haptoglobin
Complement factors	Adipsyn, complement C3

**TABLE 2**  
Adiponectin and its receptors' molecular actions in the various organs of the reproductive system.

	AdipoR1 expression	AdipoR2 expression	Receptor mRNA (PCR)	Mode of action	Endocrine effects	Immunoreactivity
Hypothalamus neurons	+	+		AMPK JAK2-STAT354	↓GnRH-driven LH release52	+
Nucleus basalis of Meynert	+50					+50
Pituitary	+50	+50		AMPK54	↓LH54 ↓GH54	+
Ovaries	+59	+59	+59		LHR ↓CYP11A1 ↓CYP17A159	+59
Theca/granulosa cells	+66	+66	+60	AMPK PPARγ66	↓P ↓A68	
Oviduct						+ in rats85
Glandular endometrium	+87	+87		AMPK87		+87
Stromal fibroblasts	+87	+87		AMPK87		
Testis	+92	+92	+ (rats, chicken Leydig cells)92,93		↓T	+ in chicken93
Trophoblast-placenta	+102	+102				
Cyneytrotrophoblast-cytotrophoblast		+	+	PPARγ		+103

Note: Superscript numbers correspond to references in text. CYP = cytochrome P; JAK = Janus kinases; STAT = signal transducers and activators of transcription; AMPK = adenosine monophosphate-activated protein kinase; PPAR = peroxisome proliferator-activated receptor; LHR = LH receptor.

TABLE 3

Adiponectin in disease and clinical disorders.

Organ	Hormone interactions	Related diseases
Hypothalamus and pituitary	LH (via GnRH) inhibition of release <sup>52</sup> Control of oxytocin-secreting neurons <sup>55</sup> GH (via ghrelin) inhibition of release <sup>56</sup>	Obesity: increased oxytocin <sup>55</sup>
Ovary	Induction of adiponectin by gonadotropins (recombinant LH) <sup>67</sup> ↓ Androgen levels as a result of increased production of adiponectin <sup>68</sup> Inhibition of P and A production <sup>68</sup>	PCOS: ↓ adiponectin in anovulatory PCOS women <sup>83</sup> ; no negative correlation between adiponectin and androgens <sup>81</sup> ; inverse correlation with CHOL, Trig1, Glu, and DBP <sup>82</sup>
Endometrium	Increased adiponectin expression in the midluteal phase (implantation) <sup>87</sup>	Endometriosis: ↑ adiponectin <sup>87</sup> Adhesion scores: inverse correlation with adiponectin <sup>87</sup> Leiomyomas: ↓ adiponectin <sup>89</sup> Endometrial cancer: ↓ adiponectin <sup>87</sup>
Placenta pregnancy	Placental contribution to maternal adiponectin <sup>105</sup> ↓ estrogens = ↓ adiponectin <sup>113</sup>	Preeclampsia: ↓ first-trimester adiponectin <sup>105</sup> GDM: ↓ adiponectin (pregnancy and postpartum) <sup>114</sup>
Fetus	Fetal source of adiponectin <sup>116</sup>	Fetuses large for placental weight: ↓ cord adiponectin <sup>118</sup> Offspring BMI: ↓ cord adiponectin levels relate to more pronounced weight gain in first 6 mo and increased BMI in 3 y <sup>119</sup> IUGR pregnancies: ↓ adiponectin <sup>121</sup>

Note: Superscript numbers correspond to references in text. BMI = body mass index; CHOL = total cholesterol; DBP = diastolic blood pressure; GDM = gestational diabetes mellitus; Glu = glucose; IUGR = intrauterine growth restriction; PCOS = polycystic ovary syndrome; Trig1 = triglycerides.