Molecular Human Reproduction, Vol.21, No.8 pp. 617–632, 2015
Advanced Access publication on May 11, 2015 doi:10.1093/molehr/gav025

molecular human reproduction

REVIEW

Direct effects of leptin and adiponectin on peripheral reproductive tissues: a critical review

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Submitted on January 14, 2015; resubmitted on April 22, 2015; accepted on May 5, 2015

ABSTRACT: Obesity is a risk factor for infertility and adverse reproductive outcomes. Adipose tissue is an important endocrine gland that secretes a host of endocrine factors, called adipokines, which modulate diverse physiologic processes including appetite, metabolism, cardiovascular function, immunity and reproduction. Altered adipokine expression in obese individuals has been implicated in the pathogenesis of a host of health disorders including diabetes and cardiovascular disease. It remains unclear whether adipokines play a significant role in the pathogenesis of adverse reproductive outcomes in obese individuals and, if so, whether the adipokines are acting directly or indirectly on the peripheral reproductive tissues. Many groups have demonstrated that receptors for the adipokines leptin and adiponectin are expressed in peripheral reproductive tissues and that these adipokines are likely, therefore, to exert direct effects on these tissues. Many groups have tested for direct effects of leptin and adiponectin on reproductive tissues including the testis, ovary, uterus, placenta and egg/embryo. The hypothesis that decreased fertility potential or adverse reproductive outcomes may result, at least in part, from defects in adipokine signaling *within* reproductive tissues has also been tested. Here, we present a critical analysis of published studies with respect to two adipokines, leptin and adiponectin, for which significant data have been generated. Our evaluation reveals significant inconsistencies and methodological limitations regarding the *direct* effects of these adipokines on peripheral reproductive tissues. We also observe a pervasive failure to account for *in vivo* data that challenge observations made *in vitro*. Overall, while leptin and adiponectin may *directly* modulate peripheral reproductive tissues, existing data suggest that these effects are minor and non-essential to human or mouse reproductive function. Current evidence suggests that direct effects of leptin or adiponectin on peripheral reproductive tissues are unlikely to factor significantly in the adverse reproductive outcomes observed in obese individuals.

Key words: leptin / adiponectin / reproduction / obesity / adipokine

Altered caloric intake during gestation impairs the health of offspring

Throughout the course of human history our survival has depended upon satisfactory harvesting of food to avoid starvation. The long-term effects of caloric restriction, including adverse health effects on offspring conceived and gestated during a time of maternal starvation, have been studied. Though not the focus of this review, caloric restriction in pregnant humans is well recognized to contribute to adult obesity and associated diseases in the offspring (Tamashiro and Moran, 2010). Babies born small for gestational age secondary to maternal caloric restriction were found, as adults, to have increased incidence of obesity, diabetes and hypertension (Hales and Barker, 1992; Painter *et al.*, 2005).

Effects of gestational caloric restriction on adult disease: animal data

Interestingly, caloric restriction in mice has been observed to enhance ovarian oocyte counts and to prolong female reproductive function when compared with mice that are not calorie-restricted (Selesniemi *et al.*, 2008). Predictably, caloric restriction in mice leads to a wide array of endocrine changes in virtually all endocrine organs including hypothalamus, pituitary, thyroid, adrenal, liver, pancreas, gut, gonads and adipose tissue (Martin *et al.*, 2008). Given the widespread endocrine changes associated with caloric restriction, it is not surprising that the mechanisms by which caloric restriction preserves or replenishes oocytes in mice are not known. Ultimately, calorie-restricted mice (and

humans) demonstrate suppression of the hypothalamic-pituitary axis leading to anovulation. It is not known whether the hypogonadotropic-hypogonadism in calorie-restricted mice plays a role in preserving ovarian reserve. Whether caloric restriction prolongs human reproductive potential remains unknown.

Notably, the ovulatory defects observed in calorie-restricted mice and sheep can be corrected with central administration of leptin, arguing that *direct* ovarian effects of leptin are not required for correction of the hypothalamic–pituitary–gonadal axis (Nagatani *et al.*, 1998; Henry *et al.*, 2001). So, although leptin administration has been shown to regulate the hypothalamic–pituitary–gonadal axis and pubertal development, a role for leptin in directly regulating peripheral reproductive organs remains to be established (Donato *et al.*, 2011; Bellefontaine *et al.*, 2014).

Adverse health effects of neonatal caloric excess

Mouse studies suggest that the early neonatal nutritional environment also affects hypothalamic programming, acting at the level of the arcuate nucleus. Leptin appears to play a neurotrophic role during the critical neonatal period of hypothalamic development and neonates of diet-induced obese rats have been shown to display abnormal organization of hypothalamic pathways that modulate neuronal responses to leptin (Bouret *et al.*, 2004, 2008). Further, both over- and under- nutrition of mouse pups during lactation is associated with perturbations in hypothalamic development, which can impair reproductive function in later adulthood (Castellano *et al.*, 2011; Caron *et al.*, 2012).

Adverse health and reproductive outcomes associated with obesity

In most of the developed and developing world, the problem of maternal over-nutrition has surpassed caloric restriction as a risk factor for metabolic diseases in affected offspring. Paradoxically, as observed for starved babies with stunted intrauterine growth, babies born from obese mothers are also predisposed to the development of obesity and associated health disorders (Guo and Jen, 1995; Ghosh *et al.*, 2001; Khan *et al.*, 2003; Armitage *et al.*, 2004; Boney *et al.*, 2005). Mechanistic studies regarding these observations are in their infancy. We do not fully understand which factors, acting on what tissues/cells, and at what time(s) during human development (i.e. during gametogenesis, antenatal, or post-natal periods), are most responsible for gestational programming of adult disease. Current data indicate neuroendocrine reprogramming of the hypothalamus and other central pathways that regulate appetite and metabolism, as well as peripheral (i.e. adipocyte) reprogramming, possibly involving leptin, insulin, and glucocorticoid pathways that are perturbed during fetal development (Tamashiro *et al.*, 2009; Spencer, 2012; Correia-Branco et al., 2015).

The prevalence of obesity, both nationally and globally, has increased dramatically over the past three decades (Stevens *et al.*, 2012). Currently, approximately one-third of adults and 17% of children in the USA are obese (defined as body mass index >30 kg/m^2) (Ogden *et al.*, 2013, 2014). Obesity increases the risk of important health problems including hypertension, type 2 diabetes, atherosclerosis, some cancers and all-cause mortality (Grundy, 2004a, b; Burke *et al.*, 2008; Prospective Studies Collaboration et al., 2009; Gonzalez and Riboli, 2010; Danaei *et al.*, 2011; Zheng *et al.*, 2011; Flegal *et al.*, 2013; Landsberg *et al.*, 2013). In addition, obesity is a risk factor for a wide array of gestational and perinatal complications that include gestational diabetes, gestational hypertension, pre-eclampsia, thromboembolism, antepartum hospitalization, Cesarean delivery, instrumental delivery, preterm delivery, shoulder dystocia, post-partum re-hospitalization, large-for-gestational age, isolated and combined congenital anomalies, miscarriage, intrauterine fetal demise, neonatal death, and neonatal admission to the neonatal intensive care unit (Cnattingius and Stephansson, 2002; Myles *et al.*, 2002; Weiss *et al.*, 2004; Cnattingius *et al.*, 2005, 2012, 2013; Nohr *et al.*, 2007; Stothard *et al.*, 2009; Blomberg and Kallen, 2010; McDonald *et al.*, 2010; Pandey *et al.*, 2010; Rankin *et al.*, 2010; Liston and Davies, 2011; Pinborg *et al.*, 2011; Sohlberg *et al.*, 2012; El-Chaar *et al.*, 2013). The pathogenesis underlying many of the adverse reproductive outcomes in obese individuals remains incompletely understood.

Adverse effects of obesity on male reproductive function

In men, there is a strong relationship between increasing BMI and reduced testosterone, sex hormone binding globulin, and free testosterone levels as well as elevated estradiol levels (Du Plessis et al., 2010; MacDonald *et al.*, 2010; Palmer *et al.*, 2012). A slim majority of studies suggests that obesity is associated with reduced sperm concentrations, but this is an inconsistent association (MacDonald *et al.*, 2010; Sermondade *et al.*, 2013). There is no consensus as to whether obesity impairs sperm motility or morphology (Palmer *et al.*, 2012). Further, it remains controversial whether male obesity is a risk factor for infertility or for reduced success rates in couples pursuing assisted reproductive technologies (Du Plessis et al., 2010; Palmer *et al.*, 2012).

Adverse effects of obesity on female reproductive function

There is emerging evidence that obesity contributes to female infertility and to reduced success with assisted reproductive technologies (Mulders *et al.*, 2003a, b; Maheshwari *et al.*, 2007). While study results have been inconsistent and study designs heterogeneous, female obesity has been associated with 25–50% reductions in pregnancy rates after *in vitro* fertilization (IVF) (Styne-Gross *et al.*, 2005; Bellver *et al.*, 2007, 2010; Robker, 2008; Robker *et al.*, 2009; Brewer and Balen, 2010; Luke *et al.*, 2011a, b). For patients undergoing IVF, excess weight (particularly morbid obesity) is associated with increased gonadotrophin requirements, higher cancelation rates, decreased follicle development and oocyte numbers, lower mean embryo grades, fewer embryos to cryopreserve, lower implantation rates, and lower live birth rates (Maheshwari *et al.*, 2007; Metwally *et al.*, 2007, 2008; Bellver *et al.*, 2010; Petersen *et al.*, 2013). Similar associations have been demonstrated in anovulatory obese women undergoing ovulation induction with gonadotrophins, wherein obesity is associated with elevated rates of cycle cancelation, reduced response to gonadotrophins, and lower rates of ovulation and pregnancy (Mulders *et al.*, 2003a). The detrimental effects of obesity on IVF success rates have been attributed to problems of oocyte/embryo quality (i.e. the 'seed') (Robker, 2008; Igosheva *et al.*, 2010; Wu *et al.*, 2010; Luke *et al.*, 2011b; Poston *et al.*, 2011; Jungheim *et al.*, 2013) as well as problems of endometrial

function (i.e. the 'soil') (Bellver *et al.*, 2007, 2010, 2011; Minge *et al.*, 2008). The underlying mechanisms by which obesity impairs ovarian/embryonic/endometrial function remain incompletely understood. Importantly, the majority of obese men and women are of normal fertility potential and experience unremarkable pregnancies and deliveries. Based upon this observation, obesity appears to be a modifier of human fertility and reproductive outcomes but is not universally associated with adverse outcomes.

Fetal programming of adult diseases

Most concerning is the emerging evidence (from animal and human data) that maternal and/or paternal obesity may 'program' offspring for increased risk of adult disorders including obesity, diabetes and atherosclerosis, while also reducing the reproductive potential of these offspring (Eriksson *et al.*, 2001; Barker, 2005, 2007; Huang *et al.*, 2007; Samuelsson *et al.*, 2008; Muhlhausler and Smith, 2009; Drake and Reynolds, 2010; Ng *et al.*, 2010; Aceti *et al.*, 2012; Cnattingius *et al.*, 2012; Fernandes *et al.*, 2012; Kim *et al.*, 2012; Barker and Thornburg, 2013a, b, Taylor *et al.*, 2014). If confirmed, these findings would indicate long-term and inter-generational health and reproductive consequences stemming from the increased prevalence of obesity. Whether these risks are reversed after weight loss remains unknown and cannot be assumed (Grayson *et al.*, 2013).

Studies in animal model systems have begun to shed light on mechanisms by which obesity impairs reproductive function. Several strains of mice are susceptible to diet-induced obesity (DIO) and obese mice generate blastocysts with reduced survival rates and abnormal embryonic cellular differentiation when compared with lean mice (Igosheva *et al.*, 2010; Jungheim and Moley, 2010; Jungheim *et al.*, 2010; Luzzo *et al.*, 2012). Additionally, embryos from diet-induced obese mice display evidence of oxidative stress with increased generation of reactive oxygen species (ROS) *in vivo* and subsequent failure to support blastocyst formation (Igosheva *et al.*, 2010; Poston *et al.*, 2011). Collectively, these studies have implicated endoplasmic reticulum stress, mitochondrial dysfunction, lipotoxicity, and insulin resistance as mediators of reproductive dysfunction in rodents and possibly in obese women (Minge *et al.*, 2008; Wu *et al.*, 2010; Jungheim *et al.*, 2011).

Are there direct effects of adipokines on the peripheral reproductive tissues?

Direct effects of adipokines on the peripheral reproductive tissues have not been shown to contribute to the pathogenesis of reproductive dysfunction in obesity. That said, numerous studies have demonstrated expression of adipokine receptors, either at the mRNA or protein levels, in each of the reproductive tissues. Additional work, generally *in vitro*, has indicated adipokine responsiveness in peripheral reproductive tissues. These studies, though sometimes inconsistent and/or incomplete, have sought to bolster the hypothesis that adipokines exert direct effects on the peripheral reproductive tissues and that alterations of adipokine expression in obesity might contribute to the adverse reproductive outcomes in this population. Below, we provide a critical appraisal of existing data regarding the direct effects of two adipokines on peripheral reproductive tissues (summarized in Table I).

The altered physiology of obesity: systemic adipokine effects

In addition to storing energy in the form of lipids, adipose tissue functions as an endocrine organ that helps to regulate appetite, metabolism and the hypothalamic–pituitary–gonadal (HPG) axis (Weisberg *et al.*, 2003; Xu *et al.*, 2003; Ahima *et al.*, 2006; Halberg *et al.*, 2008). The HPG endocrine axis is, in turn, essential for pubertal development and is the central regulator of reproductive processes in both sexes (Ouchi *et al.*, 2011; Tena-Sempere, 2012). Adipose tissue is composed of lipid-laden adipocytes, fibroblast-like pre-adipocytes, and stromovascular cells including fibroblasts, vascular endothelial cells and immune cells (principally macrophages and various T cell populations, but also NK cells, neutrophils, mast cells, and B cells). Ultimately, obesity leads to increased adipose tissue infiltration with M1 macrophages and increased inflammatory activation of these cells (Ferrante, 2007; Odegaard and Chawla, 2008, 2011). Collectively, the adipose depot secretes adipokines which exert local and systemic effects and which contribute to a chronic, low grade, inflammatory state (Weisberg *et al.*, 2003; Xu *et al.*, 2003; Grundy, 2004a, b). Obese individuals demonstrate local and systemic increases of most adipokines including tumor necrosis factor alpha (TNFα), monocyte chemoattractant protein-1 (MCP-1), leptin, retinol binding protein-4 (RBP4), interleukin-6 (IL-6), visfatin, resistin, and plasminogen activator inhibitor-1 (PAI-1) (Ouchi *et al.*, 2011; Michalakis *et al.*, 2013; Navarro and Kaiser, 2013). Obesity is associated with *reduced* expression of the anti-inflammatory proteins adiponectin and secreted frizzled-related protein 5 (Pajvani *et al.*, 2003; Tilg and Wolf, 2005).

In addition to generating the classical adipokines, adipose tissue generates and/or metabolizes autocrine/endocrine factors including growth factors, angiopoietins, steroid hormones, prostaglandins, and retinoids (Trayhurn and Wood, 2007; Waki and Tontonoz, 2007). In aggregate, these adipose tissue-derived factors have been implicated in the regulation of appetite, energy balance, immunity, angiogenesis, blood pressure, lipid metabolism, hemostasis and insulin sensitivity; altered expression of these factors in obese individuals has been implicated in the pathogenesis of diabetes, hypertension and atherosclerosis (Grundy, 2004a, b; Ouchi *et al.*, 2011). In mouse models of obesity, for example, the genetic or pharmacologic inhibition of TNFα, iNos, MCP-1, or PAI-1 activities each attenuates obesity-induced insulin resistance (Uysal *et al.*, 1997; Ruan and Lodish, 2004; Kamei *et al.*, 2006; Kanda *et al.*, 2006; Ferrante, 2007; Tamura *et al.*, 2008). This review will consider the evidence supporting *direct* effects of adipokines on peripheral reproductive organs, namely the ovary or testis, the uterus, the embryo, and the placenta. The central nervous system effects of adipokines, which are essential for normal reproductive and metabolic function, have been reviewed elsewhere and will not be addressed in this review (Ahima, 2005; Michalakis *et al.*, 2013; Navarro and Kaiser, 2013).

We recognize that established effects of obesity on reproductive organs are incompletely understood, are complex, and may include direct effects of lipids, oxidative stress, insulin/glucose metabolism, hypoxia, and altered tissue temperature (related to altered distribution of fat). Adipokines might modulate reproductive processes *indirectly*,

Table I Summary of the proposed direct effects of leptin and adiponectin on reproductive tissues; critical analysis of the supporting data (see text for details).

				Most relevant references
Adiponectin and its receptors	*General considerations*: Adiponectin null mice are viable and exhibit normal fertility. In most studies, genetic deletion of the receptors for adiponectin (Adipor1, Adipor2, or both) is not associated with subfertility. The observation that adiponectin null male and female mice can produce viable adiponectin null offspring indicates that the ovary, testis, uterus, placenta, and embryo can each function in the absence of adiponectin signaling. Maternal adiponectin levels are inversely correlated with birthweight though causation and mechanism underlying this observation remain to be established. Plasma levels of adiponectin generally range from 5 to 20 μg/ml.			Kubota *et al.* (2002), Ma *et al.* (2002), Maeda *et al.* (2002), Nawrocki *et al.* (2006), Qiao *et al.* (2012), Rosario *et al.* (2012) and Wang *et al.* (2010)
	Proposed targets	*Proposed direct effects*	*Problems and inconsistencies*	
	Theca/granulosa	Adiponectin variably enhances, suppresses, or is neutral with respect to steroidogenesis, receptor expression may be regulated by hCG, follicle concentrations may change in a menstrual cycle-dependent fashion	Supraphysiologic dosing, inconsistent findings in diverse model systems, modest effect sizes, mRNA but not protein expression changes often measured for adiponectin receptors and downstream responses to adiponectin ligand.	Ledoux *et al.* (2006), Chabrolle *et al.* (2007a, b), Lagaly *et al.* (2008), Chabrolle *et al.* (2009), Pierre *et al.* (2009) and Maillard *et al.* (2010)
	Oocyte/embryo	Adiponectin receptor expression changes with follicle development and oocyte growth, adiponectin enhances egg maturation and ovulation, adiponectin and its receptors are expressed in preimplantation embryos, possible role in implantation, elevated levels in mid-secretory phase, chronic infusion of adiponectin in pregnant mice produced intrauterine growth restriction	Inconsistent associations between follicular fluid adiponectin levels and *in vitro* fertilization outcomes. Treatment of oocyte-cumulus complexes with adiponectin *in vitro* did not affect egg maturation in bovine studies but enhanced embryonic development in mouse studies. Inconsistent effects of adiponectin on embryo development. Mechanistic studies largely not performed.	Campos *et al.* (2008), Maillard *et al.* (2010), Palin *et al.* (2012) and Richards *et al.* (2012)
	Endometrium	Adiponectin and its receptors are expressed in human endometrium and transcript levels appear to peak during the mid-luteal phase, possible role in implantation	mRNA but not protein expression changes often measured for adiponectin, adiponectin receptors, and downstream responses to ligand. Source of tissue adiponectin uncertain.	Takemura *et al.* (2006)
	Testis	Adiponectin treatment of testicular tissue/cells had variable effects on testosterone production, AdipoR2 null mice demonstrated atrophic seminiferous tubules with aspermia (lack of semen) and enlarged brains, but displayed normal testosterone levels	Inconsistent observations between research groups, supraphysiologic dosing; dose–response and time course analyses were also inconsistent and revealed modest overall treatment effects.	Bjursell *et al.* (2007), Caminos *et al.* (2008) and Martin (2014)
	Placenta	Placenta principally expresses AdipoR2 but receptor expression may depend upon gestational age; treatment of placental cells/cell lines with adiponectin altered cytokine and steroid hormone synthesis, inhibited proliferation, impaired insulin signaling, and stimulated trophoblast invasion *in vitro*	There is emerging evidence that adiponectin affects placental function and may modulate fetal growth.	Wang *et al.* (2010) and Rosario *et al.* (2012)
Leptin and its receptor (Ob-Rb)	*General considerations*: Isolated central nervous system (CNS) expression of leptin receptors restores fertility in leptin receptor null mice; ablation of agouti-related protein expressing neurons, or of global neuropeptide Y expression, or of global neuropeptide Y4 receptor expression, each partially restores fertility in leptin null mice. These observations suggest that *peripheral* leptin signaling is not essential for mouse reproduction. The observation that leptin null and leptin receptor null male and female mice can produce viable offspring (once females are induced to ovulate) indicates that the ovary, testis, uterus, placenta, and embryo can each function in the absence of leptin signaling. Plasma leptin levels generally range from 7.5 to 31 ng/ml.			Lane (1959), Batt (1972), Yokoyama *et al.* (1995), Chehab *et al.* (1996), Erickson *et al.* (1996), Malik *et al.* (2001), Chehab *et al.* (2002), Sainsbury *et al.* (2002), Ramos *et al.* (2005), Farooqi *et al.* (2007), Dubern and Clement (2012) and Wu *et al.* (2012)

Proposed targets	*Proposed direct effects*	*Problems and inconsistencies*	
Theca/granulosa	Leptin is produced in the ovary and regulates cellular proliferation and steroidogenesis	Leptin null and leptin receptor null ovaries are fully functional and generate offspring when transplanted into wild-type recipient mice, leptin null mice are fertile when stimulated with gonadotrophins, many studies with inconsistent demonstration of receptor expression at the protein level, highly inconsistent effects of ligand with respect to steroidogenesis depending upon the model system being studied, the physiologic significance of modest effects on steroidogenesis remains speculative, in most clinical studies follicular fluid leptin levels parallel serum levels (suggesting negligible local production of ligand) and levels do not correlate with fertility outcomes after *in vitro* fertilization.	Hummel (1957), Hummel *et al.* (1966), Batt (1972), Swerdloff *et al.* (1976), Swerdloff *et al.* (1978), Chehab *et al.* (1996), Cioffi *et al.* (1997), Chehab *et al.* (2002), Pineda *et al.* (2010) and Zhang *et al.* (2012)
Oocyte/embryo	Leptin variably enhances or inhibits oocyte/embryo maturation and development	Leptin receptor null and leptin null eggs can generate normal pregnancies and offspring, highly inconsistent reports regarding effects of leptin on egg/embryo maturation *in vitro*.	Karlsson *et al.* (1997), Zachow and Magoffin (1997), Agarwal *et al.* (1999), Zachow *et al.* (1999), Duggal *et al.* (2000), Spicer *et al.* (2000), Ghizzoni *et al.* (2001), Duggal *et al.* (2002a, b), Sirotkin *et al.* (2005), Ricci *et al.* (2006), Nicklin *et al.* (2007) and Karamouti *et al.* (2008)
Endometrium	Leptin is expressed in the endometrium and variably enhances or impairs embryo implantation	Leptin receptor null mice can have normal pregnancies and deliveries once hormonally induced to conceive, one human with defective/absent leptin receptors has had a child. A paucity of evidence supporting local leptin production.	de Luca *et al.* (2005)
Testis	Leptin modulates hCG-stimulated androgen production	Conflicting reports regarding Ob-Rb receptor protein expression in testis, inconsistent dose effects in rodent studies of steroidogenesis, modest effect sizes.	Fei *et al.* (1997), Caprio *et al.* (1999), Tena-Sempere *et al.* (1999) and Herrid *et al.* (2008a, b)
Placenta	Leptin modulates trophoblast proliferation and invasion *in vitro*	Studies with leptin null mating pairs indicate that embryonic, placental, and maternal leptin signaling are dispensable for reproduction *after* ovulation has been induced, leptin receptor null and leptin null eggs can generate normal pregnancies/placentae and offspring, leptin null human fetuses have unremarkable placentation, gestations and deliveries.	Masuzaki *et al.* (1997), Mounzih *et al.* (1998), Malik *et al.* (2001), Ramos *et al.* (2005), Farooqi *et al.* (2007), Magarinos *et al.* (2007), Perez-Perez *et al.* (2009) and Dubern and Clement (2012)

by modulating some or all of these processes (i.e. glucose metabolism). Further, adipokines could *directly* affect peripheral reproductive tissues or modulate the functions of resident immune cells or vascular endothelial cells. This review focuses on data supporting (or rejecting) the hypothesis that obesity-associated changes in local and systemic adipokine levels directly impact the function of peripheral reproductive tissues and negatively impact reproductive outcomes in obese individuals. We conclude that two signature adipokines, leptin and adiponectin, do not significantly contribute to the physiology of reproduction *via* direct effects on the peripheral reproductive tissues and are unlikely to contribute to adverse reproductive outcomes in obese individuals via direct effects on these target tissues.

Adiponectin: overview

Adiponectin is the most abundantly secreted protein from white adipose tissue and is a recently described 'beneficial' adipokine whose levels are *reduced* in obesity. Adiponectin is detected in serum as a low molecular weight (trimeric) complex and as higher molecular weight (hexameric and multimeric) complexes, each with variable biological activities depending upon the target tissue (Arita *et al.*, 1999; Yang *et al.*, 2001; Pajvani *et al.*, 2003). Females have 2–3 fold higher circulating levels of adiponectin than males (Pajvani *et al.*, 2003). Adiponectin improves insulin sensitivity, inhibits hepatic gluconeogenesis, and inhibits vascular inflammation (Berg *et al.*, 2001; Combs *et al.*, 2001; Yamauchi *et al.*, 2001, 2002; Stefan and Stumvoll, 2002; Berg and Scherer, 2005; Awazawa *et al.*, 2011; Okamoto, 2011; Okamoto *et al.*, 2013; Yamauchi and Kadowaki, 2013; Comninos *et al.*, 2014). Adiponectin levels are lower in obese individuals but increase with weight loss (Arita *et al.*, 1999; Yang *et al.*, 2001). Circulating adiponectin levels are inversely correlated with hyperinsulinemia and insulin resistance (Stefan and Stumvoll, 2002).

Adiponectin receptors in peripheral reproductive tissues

Adiponectin exerts its actions mainly through two receptors, AdipoR1 and AdipoR2, as well as possibly *via* the T-cadherin receptor (Hug *et al.*, 2004; Yamauchi *et al.*, 2007). Adiponectin has been shown to exert anti-inflammatory effects in macrophages and adipocytes by inhibiting nuclear factor kappa B (NFκB) transcriptional responses (Ajuwon and Spurlock, 2005). In contrast, adiponectin appears to exert pro-inflammatory responses in synovial joints and gut epithelial cells (Fayad *et al.*, 2007). In addition to cell type-specific responses, the dose and form of adiponectin exposure (monomeric versus multimeric, full length versus globular) may influence its net effects (Yamauchi *et al.*, 2003; Hug *et al.*, 2004). Whether adiponectin has pro- or anti-inflammatory effects on peripheral reproductive tissues remains to be established.

One or both of the adiponectin receptors is present in all peripheral reproductive tissues including the ovaries, oviduct, endometrium, testes, and placenta (Caminos *et al.*, 2005; Michalakis and Segars, 2010). Adiponectin's role in peripheral reproductive tissues remains unclear. Adiponectin null mice are viable and, when fertility outcomes are mentioned, appear to exhibit normal fertility (Kubota *et al.*, 2002; Ma *et al.*, 2002; Maeda *et al.*, 2002; Nawrocki *et al.*, 2006; Qiao *et al.*, 2012). Likewise, genetic deletion of the receptors for adiponectin (Adipor1, Adipor2, or both) was not associated with subfertility in one study (Yamauchi *et al.*, 2007) but loss of AdopoR2 was associated with male subfertility in another study (Lindgren *et al.*, 2013). The fact that adiponectin null male and female mice can produce viable adiponectin null offspring indicates that the ovary, testis, uterus, placenta, and embryo can each function in the absence of adiponectin signaling (Qiao *et al.*, 2012). *Together, these data support the conclusion that adiponectin signaling is non-essential to normal mouse reproduction*. That said, lack of maternal or fetal adiponectin expression did produce a host of metabolic changes in the offspring indicating non-redundant functions of this hormone with respect to mouse metabolism (Qiao *et al.*, 2012). Maternal adiponectin does not cross the placenta so any effects of maternal adiponectin on fetal development are likely to be indirect.

Because circulating adiponectin levels are naturally quite high (5–20 μg/ml) it has been difficult to genetically engineer mice that systemically over-express the hormone. Meanwhile, female transgenic mice engineered to over-express a mutated adiponectin (lacking 13 Gly-X-Y repeats in the collagenous domain of the protein) were infertile, suggesting a modulatory role for the protein with respect to reproduction (Combs *et al.*, 2004). The mechanisms underlying this infertility remain largely unexplored and 'off-target' effects of the over-expressed and mutated protein cannot be excluded. The adiponectin over-expressing mice were obese and demonstrated elevated levels of prolactin; their infertility may thus have resulted from central and/or peripheral effects of adiponectin (Combs *et al.*, 2004).

Adiponectin effects on ovarian function

Evidence supporting a peripheral response to adiponectin includes expression of the hormone and/or its receptors in ovarian granulosa and theca cells of chickens, pigs, cows, rats, and humans. Here adiponectin appears to modulate granulosa cell and theca cell steroidogenesis albeit with inconsistent findings (i.e. variably enhancing, suppressing, or neutral with respect to steroidogenesis, depending upon the model systems being tested) (Ledoux *et al.*, 2006; Chabrolle *et al.*, 2007a, b, 2009; Lagaly *et al.*, 2008; Pierre *et al.*, 2009; Maillard *et al.*, 2010). Human cumulus granulosa cells express AdopoR1 and AdipoR2 proteins, but little if any adiponectin (Richards *et al.*, 2012). AdopoR1 and AdipoR2 expression appear to be enhanced by hCG in rat granulosa cells (Chabrolle *et al.*, 2007b). In gonadotrophin-stimulated cycles in humans, LH was shown to enhance follicular fluid concentrations of adiponectin (Gutman *et al.*, 2009). In aggregate, these data indicate potential endocrine, paracrine, and autocrine roles for adiponectin in modulating ovarian function. That said, given the broad inconsistencies in the literature (complicated by diverse model species, cell systems, culture milieus (i.e. co-stimulation with luteinizing hormone or insulin), and variable adiponectin source/dosage/time course), the net effects of adiponectin on ovarian cell physiology remain controversial and of uncertain clinical significance. Recall that adiponectin signaling is not essential for mouse reproduction (Kubota *et al.*, 2002; Ma *et al.*, 2002; Maeda *et al.*, 2002; Nawrocki *et al.*, 2006; Qiao *et al.*, 2012).

Hypoadiponectinemia has been suggested to play a role in the pathogenesis the Polycystic Ovary Syndrome (PCOS) with some authors suggesting disordered ovarian response to adiponectin in affected patients (Sieminska *et al.*, 2004; Escobar-Morreale *et al.*, 2006; Campos *et al.*,

2008; Toulis *et al.*, 2009). To date, experimental data supporting a direct role for adiponectin on ovarian function have been limited to animal and *in vitro* studies. Whether adiponectin represents an important and direct regulator of ovarian function in lean or obese individuals remains to be established.

While AdipoR1 and AdipoR2 have been detected in primary follicles and antral follicles, treatment of oocyte-cumulus complexes with adiponectin *in vitro* did not affect embryo development in bovine studies (Maillard *et al.*, 2010; Palin *et al.*, 2012) but enhanced embryonic development in mouse studies (Richards *et al.*, 2012). A role for adiponectin in modulating early oocyte/embryo development remains incompletely studied.

Adiponectin effects on uterine function

Adiponectin and its receptors are expressed in human endometrium and transcript levels appear to peak during the mid-luteal phase (Takemura *et al.*, 2006). Human endometrial stromal or epithelial cells treated with supraphysiologic (50 μg/ml) dosages of adiponectin demonstrated altered phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and reduced production of Interleukin-6, Interleukin-8, and Monocyte chemotactic protein-1 (MCP1) in response to Interleukin-1β co-stimulation (Takemura *et al.*, 2006). Further investigation is needed in determine the role(s) of adiponectin signaling on endometrial function in health and disease.

Adiponectin effects on placental function

While initial reports indicated adiponectin expression in human placenta (Caminos *et al.*, 2005; Chen *et al.*, 2006), recent studies suggest that the human placenta does *not* express significant quantities of adiponectin, expresses *transcripts* for AdipoR1 and AdipoR2, but principally expresses AdiopR2 at the protein level (Corbetta *et al.*, 2005; McDonald and Wolfe, 2009; Tie *et al.*, 2009). Fetal adiponectin is expressed in muscle and gut, and is detectable in fetal umbilical cord serum by 24 weeks of gestation (Wang *et al.*, 2010). Treatment of placental cytotrophoblasts with adiponectin modulated steroidogenic and cytokine gene expression (Lappas *et al.*, 2005; McDonald and Wolfe, 2009). Further, chronic infusion of adiponectin in pregnant mice produced intrauterine growth restriction and neonatal umbilical cord levels were inversely correlated with birthweight in humans (Wang *et al.*, 2010; Rosario *et al.*, 2012). Whether, and by what mechanism, the inverse association between gestational exposure to adiponectin and intrauterine growth plays a role in the pathogenesis of macrosomia or fetal growth restriction in humans remains to be established.

Adiponectin effects on testicular function

Adiponectin receptors are expressed in human testes including the Leydig cells but also in the epididymis, and spermatozoa, and the ligand may be expressed in Leydig cells (Caminos *et al.*, 2008; Martin, 2014). Adiponectin treatment of rat testicular tissue reduced testosterone production but did not modulate anti-Mullerian hormone (AMH) transcript levels (Caminos *et al.*, 2008). AdipoR2 null mice demonstrated atrophic seminiferous tubules with aspermia (lack of semen) and enlarged brains, but displayed normal testosterone levels; whether these testicular defects reflect central or peripheral responses to the loss of AdipoR2 signaling remains unknown (Bjursell *et al.*, 2007). The significance of these effects with respect to male fertility in lean or obese individuals remains unclear. Thus, while adiponectin signaling appears to be present in male gonadal tissue, the extent to which this signaling contributes to normal testicular function and fertility potential in lean or obese individuals, remains unclear.

Adiponectin: summary of effects on peripheral reproductive tissues

In summary, there is agreement that one or both of the receptors for adiponectin is expressed at the protein level in human endometrium, ovary, testis and placenta. Whether *via* autocrine, paracrine, or endocrine pathways, it is also certain that these tissues are exposed to adiponectin ligand. Far less is understood regarding adiponectin signaling in the function of the reproductive organs or the feto-placental unit in lean or obese individuals. Mouse data suggest that there is no requirement for adiponectin signaling in normal reproduction although excessive exposure to adiponectin may impair reproduction in female mice (Table I). Emerging data suggest a role for adiponectin in modulating peripheral reproductive tissues and reproductive outcomes, most notably affecting fetal growth during gestation (Qiao *et al.*, 2012). Understanding the specific effects of adiponectin, whether insulin sensitizing or anti-inflammatory, on peripheral reproductive tissues will require additional investigation. The extent to which altered adiponectin tone *directly* modulates peripheral reproductive/embryonic tissues or contributes to adverse reproductive performance in obesity (or after caloric restriction) remains unclear.

Leptin: overview

Leptin is the 167 amino acid protein encoded by the *LEP* (a.k.a. *OB*) gene. Leptin regulates food intake, energy expenditure, fat storage, immune function and insulin signaling (Ahima *et al.*, 2006). Leptin is expressed principally in adipocytes and, to a lesser extent, in the intestines, skeletal muscle, placental syncytiotrophoblasts, and possibly the ovary (Hassink *et al.*, 1997; Masuzaki *et al.*, 1997; Perez-Perez *et al.*, 2009). Peripheral leptin levels correlate with fat mass and body mass index (BMI); levels range from means of 7.5 ng/ml in lean individuals to 31.3 ng/ml in obese individuals (Considine *et al.*, 1996; Carlsson *et al.*, 1997). Leptin receptors are present centrally in several hypothalamic nuclei (including the arcuate nucleus) where leptin plays essential roles in regulating appetite, metabolism, pubertal development and gonadotrophin secretion (Tartaglia *et al.*, 1995; Chehab *et al.*, 2002).

The reproductive phenotype of leptin null mice

Leptin null and leptin receptor null mice exhibit low gonadotrophin concentrations, immature reproductive organs, and impaired sexual

maturation which is restored in leptin null mice with exogenous administration of leptin (Hummel, 1957; Batt, 1972; Swerdloff *et al.*, 1976, 1978; Mounzih *et al.*, 1997; Chehab *et al.*, 2002). Leptin and leptin receptor gene defects are rare causes of human obesity and cannot explain delayed puberty, oligo-anovulation, or subfertility in most human populations (Dubern and Clement, 2012).

When leptin deficient male mice are diet-restricted (i.e. lean) some remain fertile, in contrast to lean leptin deficient females which are uniformly infertile (Lane and Dickie, 1954; Swerdloff *et al.*, 1976). We can therefore conclude that leptin signaling, both central and peripheral, is not strictly required for male mouse reproductive function.

Peripheral leptin is not required for ovarian function or establishment of pregnancy

Once ovulatory dysfunction is overcome in obese or lean leptin null female mice (i.e. via LH+FSH stimulation of leptin null females), normal pregnancy and parturition can proceed (Lane, 1959; Batt, 1972; Yokoyama *et al.*, 1995; Chehab *et al.*, 1996, 2002). Likewise, early studies revealed that leptin null and leptin receptor null ovaries are fully functional when transplanted into wild-type recipient mice, demonstrating that intraovarian leptin production and signaling is dispensable for female mouse reproduction and that ovaries devoid of leptin signaling respond normally to gonadotrophins (Hummel, 1957; Hummel *et al.*, 1966; Batt, 1972; Swerdloff *et al.*, 1976, 1978; Chehab *et al.*, 1996, 2002; Pineda *et al.*, 2010; Zhang *et al.*, 2012) (Table I).

Elegant studies have formally tested pregnancy outcomes in which *no* embryonic, placental, or maternal leptin signaling is present after conception: leptin null females and males were mated (while replete with exogenous leptin), followed by early withdrawal of exogenous leptin treatments. Absence of leptin did not impair reproductive success (though the pregnant mice became more obese), indicating that neither fat-derived nor placentally-derived leptin is required to sustain mouse embryonic development once embryo implantation has occurred (Mounzih *et al.*, 1998). These observations contrast with reports suggesting that leptin is required for embryo implantation but not thereafter (Malik *et al.*, 2001; Ramos *et al.*, 2005). Some of the reported responses to leptin treatment could represent off target effects (i.e. Leukemia Inhibitory Factor receptor effects) of the leptin receptor blocking peptides employed; studies for which detailed molecular analyses including proof of specificity were not presented (Gonzalez and Leavis, 2003; Ramos *et al.*, 2005).

Meanwhile, compelling human and mouse data demonstrate convincingly that peripheral leptin signaling is not required for embryo implantation. Recall that the db/db mouse, which is incapable of transmitting leptin signaling, is developmentally normal *in utero* and after birth, indicating that placental/embryonic leptin signaling is not required for normal placentation or development in mice (though it is essential for body weight management and pubertal development). When leptin receptor signaling was restored only in the neurons of leptin receptor deficient mice (db/db), fertility was restored: these data indicate that peripheral leptin receptor signaling (i.e. ovarian, uterine) is not essential to mouse reproduction (de Luca *et al.*, 2005). Likewise, ablation of agouti-related protein expressing neurons, or of global neuropeptide Y expression, or of global neuropeptide Y4 receptor expression, each partially restored fertility in leptin null mice, indicating that peripheral leptin signaling is unlikely to be required for fertility in male or female mice (Erickson *et al.*, 1996; Sainsbury *et al.*, 2002; Wu *et al.*, 2012).

Leptin acts centrally to modulate reproduction: leptin deficient humans

Humans that are leptin or leptin receptor deficient demonstrate the expected metabolic and endocrine defects, as well as T cell immune defects, but reveal otherwise normal gestational and post-natal development (Farooqi *et al.*, 2007; Dubern and Clement, 2012). A handful of leptin receptor mutations/truncations have now been described in humans, each of which demonstrates delayed puberty and clinical hypogonadism of variable severity (Farooqi *et al.*, 2007). Together, these human data indicate that placental leptin production and placental leptin signaling cascades are not essential for normal establishment and progression of pregnancy. In addition, one woman with defective leptin receptors (lacking the transmembrane and intracellular signaling domains of the receptor), while unusual in that she underwent pubertal development, albeit delayed, was able to conceive spontaneously and to deliver a healthy baby, raising considerable questions about the requirements for leptin signaling in normal ovarian and endometrial functions (Nizard *et al.*, 2012).

Together, the preponderance of evidence indicates that the neuroendocrine effects of leptin account for the sterility of leptin null mice (lep−/−) and leptin receptor null mice (lepr−/−) and humans. Such observations do not, however, preclude the hormone from modulating the functions of peripheral reproductive tissues in lean or obese humans. Below, we address the evidence that leptin directly regulates ovarian function, oocyte maturation, embryo development, embryo implantation and placental function.

Leptin effects on ovarian function

Serum leptin levels vary with the phases of the menstrual cycle and peak in the luteal phase (Hardie *et al.*, 1997). While early reports suggested that leptin is expressed in the ovary, oocyte and early embryo, these studies focused on mRNA expression and were non-quantitative (Cioffi *et al.*, 1997). Where immunofluorescent/immunohistochemical staining was performed on reproductive tissues, there remained no way to determine the source of the leptin that was detected and important experimental controls were lacking (Antczak *et al.*, 1997; Cioffi *et al.*, 1997; Loffler *et al.*, 2001; Basak and Duttaroy, 2012). Thus, while it remains possible that leptin is generated in the ovary/corpus luteum, no recent studies have elaborated on the clinical significance, if any, of ovary-derived leptin. In most studies, follicular fluid leptin levels parallel serum levels and no consistent association has been drawn between these levels and *in vitro* fertilization (IVF) success rates (Dorn *et al.*, 2003; Chen *et al.*, 2004; Wunder *et al.*, 2005; Hill *et al.*, 2007; Takikawa *et al.*, 2010; Almog *et al.*, 2011).

What are the data supporting a role for leptin in modulating ovarian function? Leptin has been shown to exert effects on ovarian theca and granulosa cells as well as on cells in the oviduct, the endometrium, and the developing embryo. Specifically, leptin has been shown to modulate steroidogenesis and to influence embryo development, though many

studies employed supraphysiologic leptin dosing, findings were broadly inconsistent, and the magnitude of many of the measured changes was often marginal (Karlsson *et al.*, 1997; Zachow and Magoffin, 1997; Agarwal *et al.*, 1999; Zachow *et al.*, 1999; Duggal *et al.*, 2000, 2002a, b; Spicer *et al.*, 2000; Ghizzoni *et al.*, 2001; Sirotkin *et al.*, 2005; Ricci *et al.*, 2006; Nicklin *et al.*, 2007; Karamouti *et al.*, 2008). The importance of these leptin effects with respect to human reproductive performance remains uncertain. While enhancing our understanding of steroid hormone synthesis remains intellectually worthwhile, infertility, *per se*, as well as adverse reproductive outcomes, have not been linked to mild impairments in steroidogenesis. The reader is reminded that studies in leptin and leptin receptor null mice have indicated that adipose tissue/ovarian/embryonic and placental effects of leptin are *not* essential for normal mouse embryologic/gestational development (Mounzih *et al.*, 1998; Zhang *et al.*, 2012). Further, successful donor egg cycles in oophorectomized women indicate that any granulosa/theca cell-derived leptin (Cioffi *et al.*, 1997) is similarly dispensable for *sustaining* human pregnancies when supplemental estrogen and progesterone are provided to oocyte/embryo recipients. Apart from estrogen and progesterone, no ovarian products (adipokine or otherwise) are required to initiate or sustain normal human embryo implantation, placentation, and pregnancy.

Leptin effects on placental function

Meanwhile, leptin is produced by the placenta and leptin levels rise during pregnancy (Masuzaki *et al.*, 1997). Supraphysiologic leptin concentrations applied to choriocarcinoma cells stimulated their proliferation and survival, suggesting autocrine effects of placentally-derived leptin (Masuzaki *et al.*, 1997; Magarinos *et al.*, 2007; Perez-Perez *et al.*, 2009). Similarly, supraphysiologic concentrations of leptin (100 ng/ml) enhanced placental cytokine production (Lappas *et al.*, 2005). The physiologic significance of placental leptin production remains unclear in light of the observation that leptin signaling is not required for normal intrauterine development in humans or mice (Mounzih *et al.*, 1998; Zhang *et al.*, 2012). It has been proposed that placental leptin modulates maternal appetite and metabolism during pregnancy, just as adipose tissue-derived leptin does outside of gestation (Mounzih *et al.*, 1998).

Leptin effects on testicular function

Leptin and leptin receptor transcripts have been detected in testicular cells suggesting the potential for leptin to directly modulate testicular functions: unfortunately, no consensus exists regarding whether full-length leptin receptors (i.e. the Ob-Rb receptors capable of leptin signal transduction) are expressed in the testis at the protein level (Tena-Sempere *et al.*, 1999; Herrid *et al.*, 2008a, b). Whereas leptin receptor isoforms can be detected in many tissues by RT–PCR, no receptor mRNA isoforms are detectable in testis by Northern blot analysis (Fei *et al.*, 1997). Although it was observed that 30–90 min (but not 24 h) leptin treatments of rat Leydig cells modulated hCG-stimulated androgen production, this remains an effect without clear clinical significance (Caprio *et al.*, 1999), particularly in light of conflicting reports regarding receptor expression in these cells (Herrid *et al.*, 2008a). Similar effects were observed in isolated rat testes, though modest in magnitude, and without a discernable dose response (Tena-Sempere *et al.*, 1999).

Leptin: summary of effects on peripheral reproductive tissues

What, then, can be concluded from the vast number of studies demonstrating leptin responsiveness in ovarian, endometrial, embryonic, placental, and testicular tissues? The majority of studies are constrained by significant methodologic limitations: most employ supraphysiologic leptin dosing, demonstrate inconsistent dose responses to leptin treatment, and neglect to demonstrate leptin production or full length leptin receptor (OB-Rb) expression at the protein level (by Western blot or by well-controlled immunohistochemistry). Whether there is functional redundancy in leptin signaling, or whether leptin performs non-essential functions in placental and embryonic development remains to be fully established. Redundancy of 'thrifty' gene functions is suggested by the disappointing results of clinical trials in which leptin administration was tested for weight loss in obese individuals: leptin supplementation is, apparently, unable to overcome the host of adaptations collectively engineered to protect and enhance caloric intake (Heymsfield *et al.*, 1999; Hukshorn *et al.*, 2002). In summary, direct leptin signaling cascades in the testis, ovary, uterus, placenta, and embryo appear to be non-essential to mouse and human reproductive function (Gonzalez and Leavis, 2001; Tanaka and Umesaki, 2008; Dos Santos *et al.*, 2012; Dubern and Clement, 2012).

Conclusions

Because the placenta and fetus are *both* of fetal origin, any adipokine receptor null mice that are viable argue for non-essential roles for that adipokine in early embryo development, later embryo implantation and placentation, and final fetal development. Similarly, fertile adipokine null or receptor null mice indicate the non-essential role of that adipokine with regard to sperm production as well as follicle recruitment, ovulation, fertilization, and endometrial embryo receptivity. Based upon the reproductive phenotypes of leptin null and leptin receptor null mice, which can be made fertile if pubertal development and gonadotrophin levels are restored (which is possible *via* a host of central nervous system genetic or pharmacologic manipulations, and by gonadal transplantation), we conclude that leptin production from the placenta or embryo, and leptin signaling in the ovary, testis, placenta, uterus, and fetus are not required for mouse reproduction. Humans that lack leptin or the leptin receptor are similarly viable and at least one woman lacking functional leptin receptors was able to reproduce. While leptin may *directly* modulate peripheral reproductive tissues, current evidence indicates that the principal effects of leptin with respect to reproductive performance are *indirect* effects.

Similar reasoning can be applied to adiponectin and its receptors: while the peripheral reproductive tissues are bathed in the adiponectin ligand and many peripheral reproductive tissues express adiponectin receptors, no compelling evidence indicates that direct effects of adiponectin are essential for normal mouse reproduction. While adiponectin may directly modulate peripheral reproductive tissues, current evidence

indicates that the principal effects of adiponectin with respect to reproductive performance are likely to be *indirect* effects.

Although the majority of obese women will have favorable reproductive outcomes, emerging evidence in animal models and humans indicates a significantly elevated risk of subfertility and adverse prenatal, perinatal, and post-natal outcomes among obese women and their offspring as compared with lean counterparts. The reproductive problems associated with obesity are real; the pathogenesis of these problems remains poorly understood. Because obesity leads to perturbations in adipokine expression, and adipokine receptors are expressed in reproductive tissues, there has been a biologically plausible rationale for testing the effects of adipokines on peripheral reproductive tissues.

With respect to the highly tested adipokines leptin and adiponectin, many of the studies have been sub-optimally designed, executed, and interpreted (lacking suitable positive and negative control cells/tissues, physiologic hormone dosages, dose response and time course analyses, *bona fide* antibodies, protein loading controls, and quantitative methods at the mRNA and protein levels). Results from many studies have been inconsistent and sometimes contradictory. A cursory review of the literature perpetuates an overly exuberant conclusion that leptin and adiponectin *must* exert important effects directly on peripheral reproductive tissues. A critical analysis of published data, including mouse and human data, suggests that the principal effects of leptin and adiponectin on peripheral reproductive tissues are most likely indirect and that, while perturbations of leptin and adiponectin expression in obese individuals may adversely affect reproductive outcomes, these effects appear to be modest.

Authors' roles

This manuscript was researched, written, discussed and edited by all three authors (J.F.K., R.S. and C.B.K.); the Table was created by J.F.K. and C.B.K.

Funding

This work was supported by National Institutes of Health grants R01-HL105490 (R.S.) and R01-DK091841 (C.B.K.).

Conflict of interest

None declared.

References

Aceti A, Santhakumaran S, Logan KM, Philipps LH, Prior E, Gale C, Hyde MJ, Modi N. The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-analysis. *Diabetologia* 2012;**55**:3114–3127.

Agarwal SK, Vogel K, Weitsman SR, Magoffin DA. Leptin antagonizes the insulin-like growth factor-I augmentation of steroidogenesis in granulosa and theca cells of the human ovary. *J Clin Endocrinol Metab* 1999;**84**:1072–1076.

Ahima RS. Central actions of adipocyte hormones. *Trends Endocrinol Metab* 2005;**16**:307–313.

Ahima RS, Qi Y, Singhal NS. Adipokines that link obesity and diabetes to the hypothalamus. *Prog Brain Res* 2006;**153**:155–174.

Ajuwon KM, Spurlock ME. Adiponectin inhibits LPS-induced NF-kappaB activation and IL-6 production and increases PPARgamma2 expression in adipocytes. *Am J Physiol Regul Integr Comp Physiol* 2005;**288**:R1220–5.

Almog B, Azem F, Kapustiansky R, Azolai J, Wagman I, Levin I, Hauser R, Pauzner D, Lessing JB, Amit A *et al.* Intrafollicular and serum levels of leptin during in vitro fertilization cycles: comparison between the effects of recombinant follicle-stimulating hormones and human menopausal gonadotrophin. *Gynecol Endocrinol* 2011;**27**:666–668.

Antczak M, Van Blerkom J, Clark A. A novel mechanism of vascular endothelial growth factor, leptin and transforming growth factor-beta2 sequestration in a subpopulation of human ovarian follicle cells. *Hum Reprod* 1997;**12**:2226–2234.

Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K *et al.* Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999;**257**:79–83.

Armitage JA, Khan IY, Taylor PD, Nathanielsz PW, Poston L. Developmental programming of the metabolic syndrome by maternal nutritional imbalance: how strong is the evidence from experimental models in mammals? *J Physiol* 2004;**561**:355–377.

Awazawa M, Ueki K, Inabe K, Yamauchi T, Kubota N, Kaneko K, Kobayashi M, Iwane A, Sasako T, Okazaki Y *et al.* Adiponectin enhances insulin sensitivity by increasing hepatic IRS-2 expression via a macrophage-derived IL-6-dependent pathway. *Cell Metab* 2011;**13**:401–412.

Barker DJ. The developmental origins of insulin resistance. *Horm Res.* 2005;**64**(Suppl 3):2–7.

Barker DJ. The origins of the developmental origins theory. *J Intern Med* 2007;**261**:412–417.

Barker DJ, Thornburg KL. The obstetric origins of health for a lifetime. *Clin Obstet Gynecol* 2013a;**56**:511–519.

Barker DJ, Thornburg KL. Placental programming of chronic diseases, cancer and lifespan: a review. *Placenta* 2013b;**34**:841–845.

Basak S, Duttaroy AK. Leptin induces tube formation in first-trimester extravillous trophoblast cells. *Eur J Obstet Gynecol Reprod Biol* 2012;**164**:24–29.

Batt RA. The response of the reproductive system in the female mutant mouse, obese (genotype obob) to gonadotrophin-releasing hormones. *J Reprod Fertil* 1972;**31**:496–497.

Bellefontaine N, Chachlaki K, Parkash J, Vanacker C, Colledge W, d'Anglemont de Tassigny X, Garthwaite J, Bouret SG, Prevot V. Leptin-dependent neuronal NO signaling in the preoptic hypothalamus facilitates reproduction. *J Clin Invest* 2014;**124**:2550–2559.

Bellver J, Melo MA, Bosch E, Serra V, Remohi J, Pellicer A. Obesity and poor reproductive outcome: the potential role of the endometrium. *Fertil Steril* 2007;**88**:446–451.

Bellver J, Ayllon Y, Ferrando M, Melo M, Goyri E, Pellicer A, Remohi J, Meseguer M. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. *Fertil Steril* 2010;**93**:447–454.

Bellver J, Martinez-Conejero JA, Labarta E, Alama P, Melo MA, Remohi J, Pellicer A, Horcajadas JA. Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome. *Fertil Steril* 2011;**95**:2335–2341, 41 e1–8.

Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res* 2005;**96**:939–949.

Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001;**7**:947–953.

Bjursell M, Ahnmark A, Bohlooly YM, William-Olsson L, Rhedin M, Peng XR, Ploj K, Gerdin AK, Arnerup G, Elmgren A *et al.* Opposing effects of adiponectin receptors 1 and 2 on energy metabolism. *Diabetes* 2007;**56**:583–593.

Blomberg MI, Kallen B. Maternal obesity and morbid obesity: the risk for birth defects in the offspring. *Birth Defects Res A Clin Mol Teratol* 2010;**88**:35–40.

Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005;**115**:e290–e296.

Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science* 2004;**304**:108–110.

Bouret SG, Gorski JN, Patterson CM, Chen S, Levin BE, Simerly RB. Hypothalamic neural projections are permanently disrupted in diet-induced obese rats. *Cell Metab* 2008;**7**:179–185.

Brewer CJ, Balen AH. The adverse effects of obesity on conception and implantation. *Reproduction* 2010;**140**:347–364.

Burke GL, Bertoni AG, Shea S, Tracy R, Watson KE, Blumenthal RS, Chung H, Carnethon MR. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med* 2008;**168**:928–935.

Caminos JE, Nogueiras R, Gallego R, Bravo S, Tovar S, Garcia-Caballero T, Casanueva FF, Dieguez C. Expression and regulation of adiponectin and receptor in human and rat placenta. *J Clin Endocrinol Metab* 2005; **90**:4276–4286.

Caminos JE, Nogueiras R, Gaytan F, Pineda R, Gonzalez CR, Barreiro ML, Castano JP, Malagon MM, Pinilla L, Toppari J *et al.* Novel expression and direct effects of adiponectin in the rat testis. *Endocrinology* 2008; **149**:3390–3402.

Campos DB, Palin MF, Bordignon V, Murphy BD. The 'beneficial' adipokines in reproduction and fertility. *Int J Obes* 2008;**32**:223–231.

Caprio M, Isidori AM, Carta AR, Moretti C, Dufau ML, Fabbri A. Expression of functional leptin receptors in rodent Leydig cells. *Endocrinology* 1999; **140**:4939–4947.

Carlsson B, Ankarberg C, Rosberg S, Norjavaara E, Albertsson-Wikland K, Carlsson LM. Serum leptin concentrations in relation to pubertal development. *Arch Dis Child* 1997;**77**:396–400.

Caron E, Ciofi P, Prevot V, Bouret SG. Alteration in neonatal nutrition causes perturbations in hypothalamic neural circuits controlling reproductive function. *J Neurosci* 2012;**32**:11486–11494.

Castellano JM, Bentsen AH, Sanchez-Garrido MA, Ruiz-Pino F, Romero M, Garcia-Galiano D, Aguilar E, Pinilla L, Dieguez C, Mikkelsen JD *et al.* Early metabolic programming of puberty onset: impact of changes in postnatal feeding and rearing conditions on the timing of puberty and development of the hypothalamic kisspeptin system. *Endocrinology* 2011;**152**:3396–3408.

Chabrolle C, Tosca L, Crochet S, Tesseraud S, Dupont J. Expression of adiponectin and its receptors (AdipoR1 and AdipoR2) in chicken ovary: potential role in ovarian steroidogenesis. *Domest Anim Endocrinol* 2007a; **33**:480–487.

Chabrolle C, Tosca L, Dupont J. Regulation of adiponectin and its receptors in rat ovary by human chorionic gonadotrophin treatment and potential involvement of adiponectin in granulosa cell steroidogenesis. *Reproduction* 2007b;**133**:719–731.

Chabrolle C, Tosca L, Rame C, Lecomte P, Royere D, Dupont J. Adiponectin increases insulin-like growth factor I-induced progesterone and estradiol secretion in human granulosa cells. *Fertil Steril* 2009;**92**:1988–1996.

Chehab FF, Lim ME, Lu R. Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. *Nat Genet* 1996;**12**:318–320.

Chehab FF, Qiu J, Mounzih K, Ewart-Toland A, Ogus S. Leptin and reproduction. *Nutr Rev* 2002;**60**:S39–S46; discussion S68–84, 5–7.

Chen R, Fisch B, Ben-Haroush A, Kaplan B, Hod M, Orvieto R. Serum and follicular fluid leptin levels in patients undergoing controlled ovarian hyperstimulation for in vitro fertilization cycle. *Clin Exp Obstet Gynecol* 2004;**31**:103–106.

Chen J, Tan B, Karteris E, Zervou S, Digby J, Hillhouse EW, Vatish M, Randeva HS. Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines. *Diabetologia* 2006;**49**:1292–1302.

Cioffi JA, Van Blerkom J, Antczak M, Shafer A, Wittmer S, Snodgrass HR. The expression of leptin and its receptors in pre-ovulatory human follicles. *Mol Hum Reprod* 1997;**3**:467–472.

Cnattingius S, Stephansson O. The epidemiology of stillbirth. *Semin Perinatol* 2002;**26**:25–30.

Cnattingius R, Hoglund B, Kieler H. Emergency cesarean delivery in induction of labor: an evaluation of risk factors. *Acta Obstet Gynecol Scand* 2005;**84**:456–462.

Cnattingius S, Villamor E, Lagerros YT, Wikstrom AK, Granath F. High birth weight and obesity—a vicious circle across generations. *Int J Obes* 2012; **36**:1320–1324.

Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikstrom AK, Granath F. Maternal obesity and risk of preterm delivery. *JAMA* 2013;**309**:2362–2370.

Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J Clin Invest* 2001;**108**:1875–1881.

Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M, Nawrocki AR, Rajala MW, Parlow AF, Cheeseboro L *et al.* A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. *Endocrinology* 2004; **145**:367–383.

Comninos AN, Jayasena CN, Dhillo WS. The relationship between gut and adipose hormones, and reproduction. *Hum Reprod Update* 2014; **20**:153–174.

Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL *et al.* Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;**334**:292–295.

Corbetta S, Bulfamante G, Cortelazzi D, Barresi V, Cetin I, Mantovani G, Bondioni S, Beck-Peccoz P, Spada A. Adiponectin expression in human fetal tissues during mid- and late gestation. *J Clin Endocrinol Metab* 2005;**90**:2397–2402.

Correia-Branco A, Keating E, Martel F. Maternal undernutrition and fetal developmental programming of obesity: the glucocorticoid connection. *Reprod Sci* 2015;**22**:138–145.

Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA *et al.* National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011;**378**:31–40.

de Luca C, Kowalski TJ, Zhang Y, Elmquist JK, Lee C, Kilimann MW, Ludwig T, Liu SM, Chua SC Jr. Complete rescue of obesity, diabetes, and infertility in db/db mice by neuron-specific LEPR-B transgenes. *J Clin Invest* 2005; **115**:3484–3493.

Donato J Jr., Cravo RM, Frazao R, Gautron L, Scott MM, Lachey J, Castro IA, Margatho LO, Lee S, Lee C *et al.* Leptin's effect on puberty in mice is relayed by the ventral premammillary nucleus and does not require signaling in Kiss1 neurons. *J Clin Invest* 2011;**121**:355–368.

Dorn C, Reinsberg J, Kupka M, van der Ven H, Schild RL. Leptin, VEGF, IGF-1, and IGFBP-3 concentrations in serum and follicular fluid of women undergoing in vitro fertilization. *Arch Gynecol Obstet* 2003; **268**:187–193.

Dos Santos E, Serazin V, Morvan C, Torre A, Wainer R, de Mazancourt P, Dieudonne MN. Adiponectin and leptin systems in human endometrium during window of implantation. *Fertil Steril* 2012;**97**:771–8 e1.

Drake AJ, Reynolds RM. Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. *Reproduction* 2010;**140**:387–398.

Du Plessis SS, Cabler S, McAlister DA, Sabanegh E, Agarwal A. The effect of obesity on sperm disorders and male infertility. *Nat Rev Urol* 2010; **7**:153–161.

Dubern B, Clement K. Leptin and leptin receptor-related monogenic obesity. *Biochimie* 2012;**94**:2111–2115.

Duggal PS, Van Der Hoek KH, Milner CR, Ryan NK, Armstrong DT, Magoffin DA, Norman RJ. The in vivo and in vitro effects of exogenous leptin on ovulation in the rat. *Endocrinology* 2000;**141**:1971–1976.

Duggal PS, Ryan NK, Van der Hoek KH, Ritter LJ, Armstrong DT, Magoffin DA, Norman RJ. Effects of leptin administration and feed restriction on thecal leucocytes in the preovulatory rat ovary and the effects of leptin on meiotic maturation, granulosa cell proliferation, steroid hormone and PGE2 release in cultured rat ovarian follicles. *Reproduction* 2002a;**123**:891–898.

Duggal PS, Weitsman SR, Magoffin DA, Norman RJ. Expression of the long (OB-RB) and short (OB-RA) forms of the leptin receptor throughout the oestrous cycle in the mature rat ovary. *Reproduction* 2002b; **123**:899–905.

El-Chaar D, Finkelstein SA, Tu X, Fell DB, Gaudet L, Sylvain J, Tawagi G, Wen SW, Walker M. The impact of increasing obesity class on obstetrical outcomes. *J Obstet Gynaecol Can* 2013;**35**:224–233.

Erickson JC, Hollopeter G, Palmiter RD. Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y. *Science* 1996; **274**:1704–1707.

Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D. Size at birth, childhood growth and obesity in adult life. *Int J Obes Relat Metab Disord* 2001;**25**:735–740.

Escobar-Morreale HF, Villuendas G, Botella-Carretero JI, Alvarez-Blasco F, Sanchon R, Luque-Ramirez M, San Millan JL. Adiponectin and resistin in PCOS: a clinical, biochemical and molecular genetic study. *Hum Reprod* 2006;**21**:2257–2265.

Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, Lank E, Bottomley B, Lopez-Fernandez J, Ferraz-Amaro I *et al.* Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N Engl J Med* 2007;**356**:237–247.

Fayad R, Pini M, Sennello JA, Cabay RJ, Chan L, Xu A, Fantuzzi G. Adiponectin deficiency protects mice from chemically induced colonic inflammation. *Gastroenterology* 2007;**132**:601–614.

Fei H, Okano HJ, Li C, Lee GH, Zhao C, Darnell R, Friedman JM. Anatomic localization of alternatively spliced leptin receptors (Ob-R) in mouse brain and other tissues. *Proc Natl Acad Sci USA* 1997;**94**:7001–7005.

Fernandes C, Grayton H, Poston L, Samuelsson AM, Taylor PD, Collier DA, Rodriguez A. Prenatal exposure to maternal obesity leads to hyperactivity in offspring. *Mol Psychiatry* 2012;**17**:1159–1160.

Ferrante AW Jr. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *J Intern Med* 2007;**262**:408–414.

Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;**309**:71–82.

Ghizzoni L, Barreca A, Mastorakos G, Furlini M, Vottero A, Ferrari B, Chrousos GP, Bernasconi S. Leptin inhibits steroid biosynthesis by human granulosa-lutein cells. *Horm Metab Res* 2001;**33**:323–328.

Ghosh P, Bitsanis D, Ghebremeskel K, Crawford MA, Poston L. Abnormal aortic fatty acid composition and small artery function in offspring of rats fed a high fat diet in pregnancy. *J Physiol* 2001;**533**:815–822.

Gonzalez RR, Leavis P. Leptin upregulates beta3-integrin expression and interleukin-1beta, upregulates leptin and leptin receptor expression in human endometrial epithelial cell cultures. *Endocrine* 2001;**16**:21–28.

Gonzalez RR, Leavis PC. A peptide derived from the human leptin molecule is a potent inhibitor of the leptin receptor function in rabbit endometrial cells. *Endocrine* 2003;**21**:185–195.

Gonzalez CA, Riboli E. Diet and cancer prevention: contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur J Cancer* 2010;**46**:2555–2562.

Grayson BE, Schneider KM, Woods SC, Seeley RJ. Improved rodent maternal metabolism but reduced intrauterine growth after vertical sleeve gastrectomy. *Sci Transl Med* 2013;**5**:199ra12.

Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. *J Clin Endocrinol Metab* 2004a;**89**:2595–2600.

Grundy SM. What is the contribution of obesity to the metabolic syndrome? *Endocrinol Metab Clin North Am* 2004b;**33**:267–282, table of contents.

Guo F, Jen KL. High-fat feeding during pregnancy and lactation affects offspring metabolism in rats. *Physiol Behav* 1995;**57**:681–686.

Gutman G, Barak V, Maslovitz S, Amit A, Lessing JB, Geva E. Recombinant luteinizing hormone induces increased production of ovarian follicular adiponectin in vivo: implications for enhanced insulin sensitivity. *Fertil Steril* 2009;**91**:1837–1841.

Halberg N, Wernstedt-Asterholm I, Scherer PE. The adipocyte as an endocrine cell. *Endocrinol Metab Clin North Am* 2008;**37**:753–768, x–xi.

Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;**35**:595–601.

Hardie L, Trayhurn P, Abramovich D, Fowler P. Circulating leptin in women: a longitudinal study in the menstrual cycle and during pregnancy. *Clin Endocrinol* 1997;**47**:101–106.

Hassink SG, de Lancey E, Sheslow DV, Smith-Kirwin SM, O'Connor DM, Considine RV, Opentanova I, Dostal K, Spear ML, Leef K *et al.* Placental leptin: an important new growth factor in intrauterine and neonatal development? *Pediatrics* 1997;**100**:E1.

Henry BA, Goding JW, Tilbrook AJ, Dunshea FR, Clarke IJ. Intracerebroventricular infusion of leptin elevates the secretion of luteinising hormone without affecting food intake in long-term food-restricted sheep, but increases growth hormone irrespective of bodyweight. *J Endocrinol* 2001;**168**:67–77.

Herrid M, O'Shea T, McFarlane JR. Ontogeny of leptin and its receptor expression in mouse testis during the postnatal period. *Mol Reprod Dev* 2008a;**75**:874–880.

Herrid M, Xia Y, O'Shea T, McFarlane JR. Leptin inhibits basal but not gonadotrophin-stimulated testosterone production in the immature mouse and sheep testis. *Reprod Fertil Dev* 2008b;**20**:519–528.

Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane J, Self B, Hunt P *et al.* Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* 1999;**282**:1568–1575.

Hill MJ, Uyehara CF, Hashiro GM, Frattarelli JL. The utility of serum leptin and follicular fluid leptin, estradiol, and progesterone levels during an in vitro fertilization cycle. *J Assist Reprod Genet* 2007;**24**:183–188.

Huang JS, Lee TA, Lu MC. Prenatal programming of childhood overweight and obesity. *Matern Child Health J* 2007;**11**:461–473.

Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Natl Acad Sci USA* 2004;**101**:10308–10313.

Hukshorn CJ, van Dielen FM, Buurman WA, Westerterp-Plantenga MS, Campfield LA, Saris WH. The effect of pegylated recombinant human leptin (PEG-OB) on weight loss and inflammatory status in obese subjects. *Int J Obes Relat Metab Disord* 2002;**26**:504–509.

Hummel KP. Transplantation of ovaries of the obese mice. *Anat Rec* 1957; **128**:569.

Hummel KP, Dickie MM, Coleman DL. Diabetes, a new mutation in the mouse. *Science* 1966;**153**:1127–1128.

Igosheva N, Abramov AY, Poston L, Eckert JJ, Fleming TP, Duchen MR, McConnell J. Maternal diet-induced obesity alters mitochondrial activity and redox status in mouse oocytes and zygotes. *PLoS One* 2010;**5**:e10074.

Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. *Am J Obstet Gynecol* 2010;**203**:525–530.

Jungheim ES, Schoeller EL, Marquard KL, Louden ED, Schaffer JE, Moley KH. Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. *Endocrinology* 2010;**151**:4039–4046.

Jungheim ES, Macones GA, Odem RR, Patterson BW, Lanzendorf SE, Ratts VS, Moley KH. Associations between free fatty acids, cumulus oocyte complex morphology and ovarian function during in vitro fertilization. *Fertil Steril* 2011;**95**:1970–1974.

Jungheim ES, Schon SB, Schulte MB, DeUgarte DA, Fowler SA, Tuuli MG. IVF outcomes in obese donor oocyte recipients: a systematic review and meta-analysis. *Hum Reprod* 2013;**28**:2720–2727.

Kamei N, Tobe K, Suzuki R, Ohsugi M, Watanabe T, Kubota N, Ohtsuka-Kowatari N, Kumagai K, Sakamoto K, Kobayashi M *et al*. Overexpression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance. *J Biol Chem* 2006;**281**:26602–26614.

Kanda H, Tateya S, Tamori Y, Kotani K, Hiasa K, Kitazawa R, Kitazawa S, Miyachi H, Maeda S, Egashira K *et al*. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J Clin Invest* 2006;**116**:1494–1505.

Karamouti M, Kollia P, Kallitsaris A, Vamvakopoulos N, Kollios G, Messinis IE. Growth hormone, insulin-like growth factor I, and leptin interaction in human cultured lutein granulosa cells steroidogenesis. *Fertil Steril* 2008; **90**:1444–1450.

Karlsson C, Lindell K, Svensson E, Bergh C, Lind P, Billig H, Carlsson LM, Carlsson B. Expression of functional leptin receptors in the human ovary. *J Clin Endocrinol Metab* 1997;**82**:4144–4148.

Khan IY, Taylor PD, Dekou V, Seed PT, Lakasing L, Graham D, Dominiczak AF, Hanson MA, Poston L. Gender-linked hypertension in offspring of lard-fed pregnant rats. *Hypertension* 2003;**41**:168–175.

Kim SY, Sharma AJ, Callaghan WM. Gestational diabetes and childhood obesity: what is the link? *Curr Opin Obstet Gynecol* 2012;**24**:376–381.

Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H *et al*. Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem* 2002; **277**:25863–6.

Lagaly DV, Aad PY, Grado-Ahuir JA, Hulsey LB, Spicer LJ. Role of adiponectin in regulating ovarian theca and granulosa cell function. *Mol Cell Endocrinol* 2008;**284**:38–45.

Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D, Sowers J. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment: a position paper of The Obesity Society and the American Society of Hypertension. *J Clin Hypertens* 2013;**15**:14–33.

Lane PW. The pituitary-gonad response of genetically obese mice in parabiosis with thin and obese siblings. *Endocrinology* 1959;**65**:863–868.

Lane PW, Dickie MM. Relative sterility in obese males corrected by dietary restriction. *J Hered* 1954;**45**:56–58.

Lappas M, Yee K, Permezel M, Rice GE. Release and regulation of leptin, resistin and adiponectin from human placenta, fetal membranes, and maternal adipose tissue and skeletal muscle from normal and gestational diabetes mellitus-complicated pregnancies. *J Endocrinol* 2005; **186**:457–465.

Ledoux S, Campos DB, Lopes FL, Dobias-Goff M, Palin MF, Murphy BD. Adiponectin induces periovulatory changes in ovarian follicular cells. *Endocrinology* 2006;**147**:5178–5186.

Lindgren A, Levin M, Rodrigo Blomqvist S, Wikstrom J, Ahnmark A, Mogensen C, Bottcher G, Bohlooly YM, Boren J, Gan LM *et al*. Adiponectin receptor 2 deficiency results in reduced atherosclerosis in the brachiocephalic artery in apolipoprotein E deficient mice. *PLoS One* 2013;**8**:e80330.

Liston F, Davies GA. Thromboembolism in the obese pregnant woman. *Semin Perinatol* 2011;**35**:330–334.

Loffler S, Aust G, Kohler U, Spanel-Borowski K. Evidence of leptin expression in normal and polycystic human ovaries. *Mol Hum Reprod* 2001; **7**:1143–1149.

Luke B, Brown MB, Missmer SA, Bukulmez O, Leach R, Stern JE. The effect of increasing obesity on the response to and outcome of assisted reproductive technology: a national study. *Fertil Steril* 2011a;**96**:820–825.

Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. *Hum Reprod* 2011b;**26**:245–252.

Luzzo KM, Wang Q, Purcell SH, Chi M, Jimenez PT, Grindler N, Schedl T, Moley KH. High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/brain defects. *PLoS One* 2012;**7**:e49217.

Ma K, Cabrero A, Saha PK, Kojima H, Li L, Chang BH, Paul A, Chan L. Increased beta -oxidation but no insulin resistance or glucose intolerance in mice lacking adiponectin. *J Biol Chem* 2002;**277**:34658–34661.

MacDonald AA, Herbison GP, Showell M, Farquhar CM. The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. *Hum Reprod Update* 2010; **16**:293–311.

Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y *et al*. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002; **8**:731–737.

Magarinos MP, Sanchez-Margalet V, Kotler M, Calvo JC, Varone CL. Leptin promotes cell proliferation and survival of trophoblastic cells. *Biol Reprod* 2007;**76**:203–210.

Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology—a systematic review. *Hum Reprod Update* 2007;**13**:433–444.

Maillard V, Uzbekova S, Guignot F, Perreau C, Rame C, Coyral-Castel S, Dupont J. Effect of adiponectin on bovine granulosa cell steroidogenesis, oocyte maturation and embryo development. *Reprod Biol Endocrinol* 2010;**8**:23.

Malik NM, Carter ND, Murray JF, Scaramuzzi RJ, Wilson CA, Stock MJ. Leptin requirement for conception, implantation, and gestation in the mouse. *Endocrinology* 2001;**142**:5198–5202.

Martin LJ. Implications of adiponectin in linking metabolism to testicular function. *Endocrine* 2014;**46**:16–28.

Martin B, Golden E, Carlson OD, Egan JM, Mattson MP, Maudsley S. Caloric restriction: impact upon pituitary function and reproduction. *Ageing Res Rev* 2008;**7**:209–224.

Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, Yoshimasa Y, Tanaka I, Mori T *et al*. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. *Nat Med* 1997;**3**:1029–1033.

McDonald EA, Wolfe MW. Adiponectin attenuation of endocrine function within human term trophoblast cells. *Endocrinology* 2009;**150**: 4358–4365.

McDonald SD, Han Z, Mulla S, Beyene J, Knowledge Synthesis G. Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analyses. *BMJ* 2010;**341**:c3428.

Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. *Reprod Biomed Online* 2007;**15**:532–538.

Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril* 2008;**90**:714–726.

Michalakis KG, Segars JH. The role of adiponectin in reproduction: from polycystic ovary syndrome to assisted reproduction. *Fertil Steril* 2010; **94**:1949–1957.

Michalakis K, Mintziori G, Kaprara A, Tarlatzis BC, Goulis DG. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. *Metabolism* 2013;**62**:457–478.

Minge CE, Bennett BD, Norman RJ, Robker RL. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. *Endocrinology* 2008; **149**:2646–2656.

Mounzih K, Lu R, Chehab FF. Leptin treatment rescues the sterility of genetically obese ob/ob males. *Endocrinology* 1997;**138**:1190–1193.

Mounzih K, Qiu J, Ewart-Toland A, Chehab FF. Leptin is not necessary for gestation and parturition but regulates maternal nutrition via a leptin resistance state. *Endocrinology* 1998;**139**:5259–5262.

Muhlhausler B, Smith SR. Early-life origins of metabolic dysfunction: role of the adipocyte. *Trends Endocrinol Metab* 2009;**20**:51–57.

Mulders AG, Laven JS, Eijkemans MJ, Hughes EG, Fauser BC. Patient predictors for outcome of gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility: a meta-analysis. *Hum Reprod Update* 2003a;**9**:429–449.

Mulders AG, Laven JS, Imani B, Eijkemans MJ, Fauser BC. IVF outcome in anovulatory infertility (WHO group 2)—including polycystic ovary syndrome—following previous unsuccessful ovulation induction. *Reprod Biomed Online* 2003b;**7**:50–58.

Myles TD, Gooch J, Santolaya J. Obesity as an independent risk factor for infectious morbidity in patients who undergo cesarean delivery. *Obstet Gynecol* 2002;**100**:959–964.

Nagatani S, Guthikonda P, Thompson RC, Tsukamura H, Maeda KI, Foster DL. Evidence for GnRH regulation by leptin: leptin administration prevents reduced pulsatile LH secretion during fasting. *Neuroendocrinology* 1998;**67**:370–376.

Navarro VM, Kaiser UB. Metabolic influences on neuroendocrine regulation of reproduction. *Curr Opin Endocrinol Diabetes Obes* 2013; **20**:335–341.

Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, Pang Z, Chen AS, Ruderman NB, Chen H *et al.* Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. *J Biol Chem* 2006;**281**:2654–2660.

Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. *Nature* 2010;**467**:963–966.

Nicklin LT, Robinson RS, Campbell BK, Hunter MG, Mann GE. Leptin infusion during the early luteal phase in ewes does not affect progesterone production. *Domest Anim Endocrinol* 2007;**33**:240–244.

Nizard J, Dommergues M, Clement K. Pregnancy in a woman with a leptin-receptor mutation. *N Engl J Med* 2012;**366**:1064–1065.

Nohr EA, Bech BH, Vaeth M, Rasmussen KM, Henriksen TB, Olsen J. Obesity, gestational weight gain and preterm birth: a study within the Danish National Birth Cohort. *Paediatr Perinat Epidemiol* 2007;**21**:5–14.

Odegaard JI, Chawla A. Mechanisms of macrophage activation in obesity-induced insulin resistance. *Nat Clin Pract Endocrinol Metab* 2008;**4**:619–626.

Odegaard JI, Chawla A. Alternative macrophage activation and metabolism. *Annu Rev Pathol* 2011;**6**:275–297.

Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among adults: United States, 2011–2012. *NCHS Data Brief* 2013:1–8.

Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 2014;**311**:806–814.

Okamoto Y. Adiponectin provides cardiovascular protection in metabolic syndrome. *Cardiol Res Pract* 2011;**2011**:313179.

Okamoto Y, Ishii S, Croce K, Katsumata H, Fukushima M, Kihara S, Libby P, Minami S. Adiponectin inhibits macrophage tissue factor, a key trigger of thrombosis in disrupted atherosclerotic plaques. *Atherosclerosis* 2013; **226**:373–377.

Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011;**11**:85–97.

Painter RC, Roseboom TJ, Bleker OP. Prenatal exposure to the Dutch famine and disease in later life: an overview. *Reprod Toxicol* 2005;**20**:345–352.

Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, Engel J, Brownlee M, Scherer PE. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications fpr metabolic regulation and bioactivity. *J Biol Chem* 2003;**278**:9073–9085.

Palin MF, Bordignon VV, Murphy BD. Adiponectin and the control of female reproductive functions. *Vitam Horm* 2012;**90**:239–287.

Palmer NO, Bakos HW, Fullston T, Lane M. Impact of obesity on male fertility, sperm function and molecular composition. *Spermatogenesis* 2012;**2**:253–263.

Pandey S, Pandey S, Maheshwari A, Bhattacharya S. The impact of female obesity on the outcome of fertility treatment. *J Hum Reprod Sci* 2010;**3**:62–67.

Perez-Perez A, Maymo J, Gambino Y, Duenas JL, Goberna R, Varone C, Sanchez-Margalet V. Leptin stimulates protein synthesis-activating translation machinery in human trophoblastic cells. *Biol Reprod* 2009;**81**:826–832.

Petersen GL, Schmidt L, Pinborg A, Kamper-Jorgensen M. The influence of female and male body mass index on live births after assisted reproductive technology treatment: a nationwide register-based cohort study. *Fertil Steril* 2013;**99**:1654–1662.

Pierre P, Froment P, Negre D, Rame C, Barateau V, Chabrolle C, Lecomte P, Dupont J. Role of adiponectin receptors, AdipoR1 and AdipoR2, in the steroidogenesis of the human granulosa tumor cell line, KGN. *Hum Reprod* 2009;**24**:2890–2901.

Pinborg A, Gaarslev C, Hougaard CO, Nyboe Andersen A, Andersen PK, Boivin J, Schmidt L. Influence of female bodyweight on IVF outcome: a longitudinal multicentre cohort study of 487 infertile couples. *Reprod Biomed Online* 2011;**23**:490–499.

Pineda R, Aguilar E, Pinilla L, Tena-Sempere M. Physiological roles of the kisspeptin/GPR54 system in the neuroendocrine control of reproduction. *Prog Brain Res* 2010;**181**:55–77.

Poston L, Igosheva N, Mistry HD, Seed PT, Shennan AH, Rana S, Karumanchi SA, Chappell LC. Role of oxidative stress and antioxidant supplementation in pregnancy disorders. *Am J Clin Nutr* 2011; **94**:1980S–1985S.

Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;**373**:1083–1096.

Qiao L, Yoo HS, Madon A, Kinney B, Hay WW Jr., Shao J. Adiponectin enhances mouse fetal fat deposition. *Diabetes* 2012;**61**:3199–3207.

Ramos MP, Rueda BR, Leavis PC, Gonzalez RR. Leptin serves as an upstream activator of an obligatory signaling cascade in the embryo-implantation process. *Endocrinology* 2005;**146**:694–701.

Rankin J, Tennant PW, Stothard KJ, Bythell M, Summerbell CD, Bell R. Maternal body mass index and congenital anomaly risk: a cohort study. *Int J Obes* 2010;**34**:1371–1380.

Ricci AG, Di Yorio MP, Faletti AG. Inhibitory effect of leptin on the rat ovary during the ovulatory process. *Reproduction* 2006;**132**:771–780.

Richards JS, Liu Z, Kawai T, Tabata K, Watanabe H, Suresh D, Kuo FT, Pisarska MD, Shimada M. Adiponectin and its receptors modulate granulosa cell and cumulus cell functions, fertility, and early embryo development in the mouse and human. *Fertil Steril* 2012;**98**:471–9 e1.

Robker RL. Evidence that obesity alters the quality of oocytes and embryos. *Pathophysiology* 2008;**15**:115–121.

Robker RL, Akison LK, Bennett BD, Thrupp PN, Chura LR, Russell DL, Lane M, Norman RJ. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women. *J Clin Endocrinol Metab* 2009;**94**: 1533–1540.

Rosario FJ, Schumacher MA, Jiang J, Kanai Y, Powell TL, Jansson T. Chronic maternal infusion of full-length adiponectin in pregnant mice down-regulates placental amino acid transporter activity and expression and decreases fetal growth. *J Physiol* 2012;**590**:1495–1509.

Ruan H, Lodish HF. Regulation of insulin sensitivity by adipose tissue-derived hormones and inflammatory cytokines. *Curr Opin Lipidol* 2004;**15**:297–302.

Sainsbury A, Schwarzer C, Couzens M, Jenkins A, Oakes SR, Ormandy CJ, Herzog H. Y4 receptor knockout rescues fertility in ob/ob mice. *Genes Dev* 2002;**16**:1077–1088.

Samuelsson AM, Matthews PA, Argenton M, Christie MR, McConnell JM, Jansen EH, Piersma AH, Ozanne SE, Twinn DF, Remacle C *et al.* Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming. *Hypertension* 2008;**51**:383–392.

Selesniemi K, Lee HJ, Tilly JL. Moderate caloric restriction initiated in rodents during adulthood sustains function of the female reproductive axis into advanced chronological age. *Aging Cell* 2008;**7**:622–629.

Sermondade N, Faure C, Fezeu L, Shayeb AG, Bonde JP, Jensen TK, Van Wely M, Cao J, Martini AC, Eskandar M *et al.* BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update* 2013;**19**:221–231.

Sieminska L, Marek B, Kos-Kudla B, Niedziolka D, Kajdaniuk D, Nowak M, Glogowska-Szelag J. Serum adiponectin in women with polycystic ovarian syndrome and its relation to clinical, metabolic and endocrine parameters. *J Endocrinol Invest* 2004;**27**:528–534.

Sirotkin AV, Mlyncek M, Kotwica J, Makarevich AV, Florkovicova I, Hetenyi L. Leptin directly controls secretory activity of human ovarian granulosa cells: possible inter-relationship with the IGF/IGFBP system. *Horm Res* 2005; **64**:198–202.

Sohlberg S, Stephansson O, Cnattingius S, Wikstrom AK. Maternal body mass index, height, and risks of preeclampsia. *Am J Hypertens* 2012; **25**:120–125.

Spencer SJ. Early life programming of obesity: the impact of the perinatal environment on the development of obesity and metabolic dysfunction in the offspring. *Curr Diabetes Rev* 2012;**8**:55–68.

Spicer LJ, Chamberlain CS, Francisco CC. Ovarian action of leptin: effects on insulin-like growth factor-I-stimulated function of granulosa and thecal cells. *Endocrine* 2000;**12**:53–59.

Stefan N, Stumvoll M. Adiponectin—its role in metabolism and beyond. *Horm Metab Res* 2002;**34**:469–474.

Stevens GA, Singh GM, Lu Y, Danaei G, Lin JK, Finucane MM, Bahalim AN, McIntire RK, Gutierrez HR, Cowan M *et al.* National, regional, and global trends in adult overweight and obesity prevalences. *Popul Health Metr* 2012;**10**:22.

Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 2009;**301**:636–650.

Styne-Gross A, Elkind-Hirsch K, Scott RT Jr. Obesity does not impact implantation rates or pregnancy outcome in women attempting conception through oocyte donation. *Fertil Steril* 2005;**83**:1629–1634.

Swerdloff RS, Batt RA, Bray GA. Reproductive hormonal function in the genetically obese (ob/ob) mouse. *Endocrinology* 1976;**98**:1359–1364.

Swerdloff RS, Peterson M, Vera A, Batt RA, Heber D, Bray GA. The hypothalamic-pituitary axis in genetically obese (ob/ob) mice: response to luteinizing hormone-releasing hormone. *Endocrinology* 1978; **103**:542–547.

Takemura Y, Osuga Y, Yamauchi T, Kobayashi M, Harada M, Hirata T, Morimoto C, Hirota Y, Yoshino O, Koga K *et al.* Expression of adiponectin receptors and its possible implication in the human endometrium. *Endocrinology* 2006;**147**:3203–3210.

Takikawa S, Iwase A, Goto M, Harata T, Umezu T, Nakahara T, Kobayashi H, Suzuki K, Manabe S, Kikkawa F. Assessment of the predictive value of follicular fluid insulin, leptin and adiponectin in assisted reproductive cycles. *Gynecol Endocrinol* 2010;**26**:494–499.

Tamashiro KL, Moran TH. Perinatal environment and its influences on metabolic programming of offspring. *Physiol Behav* 2010;**100**:560–566.

Tamashiro KL, Terrillion CE, Hyun J, Koenig JI, Moran TH. Prenatal stress or high-fat diet increases susceptibility to diet-induced obesity in rat offspring. *Diabetes* 2009;**58**:1116–1125.

Tamura Y, Sugimoto M, Murayama T, Ueda Y, Kanamori H, Ono K, Ariyasu H, Akamizu T, Kita T, Yokode M *et al.* Inhibition of CCR2 ameliorates insulin resistance and hepatic steatosis in db/db mice. *Arterioscler Thromb Vasc Biol* 2008;**28**:2195–2201.

Tanaka T, Umesaki N. Leptin regulates the proliferation and apoptosis of human endometrial epithelial cells. *Int J Mol Med* 2008;**22**:683–689.

Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, Deeds J *et al.* Identification and expression cloning of a leptin receptor, OB-R. *Cell* 1995;**83**:1263–1271.

Taylor PD, Samuelsson AM, Poston L. Maternal obesity and the developmental programming of hypertension: a role for leptin. *Acta Physiol* 2014;**210**:508–523.

Tena-Sempere M. Deciphering puberty: novel partners, novel mechanisms. *Eur J Endocrinol* 2012;**167**:733–747.

Tena-Sempere M, Pinilla L, Gonzalez LC, Dieguez C, Casanueva FF, Aguilar E. Leptin inhibits testosterone secretion from adult rat testis in vitro. *J Endocrinol* 1999;**161**:211–218.

Tie W, Yu H, Chen J, Wang X, Chen W, Zhou R. Expressions of adiponectin receptors in placenta and their correlation with preeclampsia. *Reprod Sci* 2009;**16**:676–684.

Tilg H, Wolf AM. Adiponectin: a key fat-derived molecule regulating inflammation. *Expert Opin Ther Targets* 2005;**9**:245–251.

Toulis KA, Goulis DG, Farmakiotis D, Georgopoulos NA, Katsikis I, Tarlatzis BC, Papadimas I, Panidis D. Adiponectin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Hum Reprod Update* 2009;**15**:297–307.

Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 2007;**92**:347.

Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* 1997;**389**:610–614.

Waki H, Tontonoz P. Endocrine functions of adipose tissue. *Annu Rev Pathol* 2007;**2**:31–56.

Wang J, Shang LX, Dong X, Wang X, Wu N, Wang SH, Zhang F, Xu LM, Xiao Y. Relationship of adiponectin and resistin levels in umbilical serum, maternal serum and placenta with neonatal birth weight. *Aust N Z J Obstet Gynaecol* 2010;**50**:432–438.

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;**112**:1796–1808.

Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, Saade G, Eddleman K, Carter SM, Craigo SD *et al.* Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. *Am J Obstet Gynecol* 2004;**190**:1091–1097.

Wu LL, Dunning KR, Yang X, Russell DL, Lane M, Norman RJ, Robker RL. High-fat diet causes lipotoxicity responses in cumulus-oocyte complexes and decreased fertilization rates. *Endocrinology* 2010; **151**:5438–5445.

Wu Q, Whiddon BB, Palmiter RD. Ablation of neurons expressing agouti-related protein, but not melanin concentrating hormone, in leptin-deficient mice restores metabolic functions and fertility. *Proc Natl Acad Sci USA* 2012;**109**:3155–3160.

Wunder DM, Kretschmer R, Bersinger NA. Concentrations of leptin and C-reactive protein in serum and follicular fluid during assisted reproductive cycles. *Hum Reprod* 2005;**20**:1266–1271.

Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA *et al*. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003; **112**:1821–1830.

Yamauchi T, Kadowaki T. Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. *Cell Metab* 2013;**17**:185–196.

Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N *et al*. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001;**7**:941–946.

Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K *et al*. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002;**8**:1288–1295.

Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J *et al*. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biol Chem* 2003;**278**:2461–2468.

Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T *et al*. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med* 2007;**13**:332–339.

Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, Chuang LM. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 2001;**86**:3815–3819.

Yokoyama M, Katsuki M, Nomura T. The creation of mouse models for human diseases associated with reproductive disturbances by in vitro fertilization and embryo transfer. *Exp Anim* 1995;**44**:139–143.

Zachow RJ, Magoffin DA. Direct intraovarian effects of leptin: impairment of the synergistic action of insulin-like growth factor-I on follicle-stimulating hormone-dependent estradiol-17 beta production by rat ovarian granulosa cells. *Endocrinology* 1997;**138**:847–850.

Zachow RJ, Weitsman SR, Magoffin DA. Leptin impairs the synergistic stimulation by transforming growth factor-beta of follicle-stimulating hormone-dependent aromatase activity and messenger ribonucleic acid expression in rat ovarian granulosa cells. *Biol Reprod* 1999;**61**:1104–1109.

Zhang Y, Hu M, Ma H, Qu J, Wang Y, Hou L, Liu L, Wu XK. The impairment of reproduction in db/db mice is not mediated by intraovarian defective leptin signaling. *Fertil Steril* 2012;**97**:1183–1191.

Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, He J, Gupta PC, Ramadas K, Tsugane S *et al*. Association between body-mass index and risk of death in more than 1 million Asians. *N Engl J Med* 2011; **364**:719–729.