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BMP4 as a Potential Molecular Link between Obesity and Female Fertility

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Review

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Abstract

Bone morphogenetic protein 4 (BMP4) is a member of the transforming growth factor β (TGF-β) superfamily. Accumulating evidence indicates that BMP4 is widely expressed in female reproductive tissues, including the ovary and endometrium. Therefore, this review summarizes the roles of BMP4 in regulating the physiological functions of the ovary and endometrium, including folliculogenesis, ovarian steroidogenesis, endometrial decidualization and regulation of maternal-foetal immunity. Notably, increasing studies revealed that BMP4 is also critically involved in obesity. Given the continuously rising prevalence of obesity worldwide, this review further summarizes emerging evidence on the role of BMP4 in adipogenesis, the shift between white adipose tissue (WAT) and brown adipose tissue (BAT) and metabolic dysregulation. To further elucidate the role of BMP4, we also summarize the expression patterns and potential mechanisms in reproductive disorders and obesity. We found that dysregulated BMP4 expression has been reported in polycystic ovary syndrome (PCOS), recurrent spontaneous abortion (RSA) and obesity, suggesting a potential molecular link between obesity and female fertility. Hence, the potential role of BMP4 between obesity and women's fertility is further discussed and may provide direction for further reproductive-related research. This hypothesis may guide further studies to explore the underlying mechanisms and their translational implications.

Introduction

Bone morphogenetic protein 4 (BMP4) is a member of the transforming growth factor-β (TGF-β) superfamily [Ref. 1]. BMP4 is expressed in the ovary and endometrium of various animals and humans, and could also be secreted by adipose tissue (AT). The role of BMP4 in ovarian function has been reviewed by our group in 2021, highlighting its involvement in follicular development and steroidogenesis [Ref. 2]. Although limited studies have investigated the effect of BMP4 on endometrial function, recent studies have increasingly investigated its roles, underscoring its important role in regulating endometrial proliferation, decidualization and the crosstalk with immune cells [Refs 3, 4, 5]. In addition, BMP4 has also been demonstrated to promote the commitment of mesenchymal stem cells (MSCs) into the adipogenic lineage [Refs 6, 7]. Moreover, BMP4 could also regulate the formation and transition between white adipose tissue (WAT) and brown adipose tissue (BAT), highlighting its broader role in adipogenesis [Refs 8, 9, 10]. Furthermore, BMP4 has been associated with metabolic abnormalities, such as insulin resistance, which is associated with obesity [Ref. 11]. Obesity is emerging as a growing public health burden worldwide. According to the recent Lancet Diabetes & Endocrinology Commission, the definition of obesity should not only rely on BMI, but be combined with at least one additional anthropometric measure, while considering age, sex and ethnicity. But if BMI is more than 40 kg/m^2, obesity could be diagnosed without further confirmation [Ref. 12]. Obesity affects an estimated 11% of men and 15% of women worldwide, with considerable variation in prevalence across regions and population groups [Ref. 13].

Obesity is often accompanied with reproductive-related diseases in women, such as polycystic ovary syndrome (PCOS), infertility, recurrent spontaneous abortion (RSA) and recurrent implantation failure (RIF) [Refs 14–18]. Women with obesity have reduced live birth rates following in vitro fertilization (IVF) treatment compared to normal-weight women [Ref. 19]. Hence, women affected by this condition frequently experience considerable mental, economic and physical impacts. Achieving successful embryo implantation requires high-quality oocytes, a functionally competent endometrium and embryo implantation within the specific window of implantation (WOI) period. This process is under strict hormonal regulation, and disturbances could lead to infertility. However, obese women often experience ovulatory abnormalities, which may be due to dysregulation of the hypothalamic–pituitary-ovarian axis [Ref. 20]. In addition, endometrial decidualization was found to be impaired in obese mice and women [Ref. 21]. And leptin, which is secreted by fat tissue, could regulate the expression of endometrial receptivity markers [Ref. 22]. This means that obesity is closely linked to female reproduction.

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Although BMP4 has been extensively studied in reproductive physiology and AT biology, its role in these two systems has largely been investigated independently. Hence, a comprehensive understanding of BMP4 signalling in obesity and reproductive disorders may shed light on the mechanism of impaired fertility in obese women, and BMP4 may be a promising target for therapeutic intervention. This review aims to summarize the roles of BMP4 in female reproductive physiology and obesity and to explore the potential connections between these two processes, highlighting research gaps in the current study.

BMP4 structure and signalling: A brief overview

BMP4 gene, located on chromosome 14q22-q23 and encodes a preproprotein which consists of three domains, including an amino-terminal signal domain, a central domain and a carboxy-terminal mature domain [Refs 23–26]. Following proteolytic processing, mature BMP4 exists as a biologically active disulfide-linked homodimer capable of binding BMP receptors [Refs 27, 28]. BMP4 exerts its function by binding to heteromeric receptor complexes on the cell surface, including type I and type II transmembrane serine/threonine kinase receptors [Refs 29, 30]. BMP4 can regulate genes through canonical or non-canonical signalling pathways. Specifically, for the canonical pathway, also known as the Smad-dependent pathway, BMP4 binds to type I and II receptors to form a heteromeric complex. The active type II receptor subsequently phosphorylates the type I receptor, which in turn phosphorylates SMAD1/5/8 (known as receptor-regulated Smads (R-Smads)) in the cytoplasm. Activated R-Smads form heteromeric complexes with Smad4 (known as the common-mediator Smads, or co-Smads), then translocate to the nucleus to regulate gene expression as transcription factors (TF) [Refs 31, 32, 33]. This process can be inhibited by Smad6 and Smad7 (known as inhibitory Smads (I-Smads)) by competitive binding to Smad or interfere with transcriptional complexes on DNA [Refs 34, 35]. In the non-canonical signalling pathway, BMP4 activates downstream pathways, including c-Jun amino terminal kinase (JNK), p38 mitogen-activated protein kinase (p38-MAPK), phosphatidylinositol 3 kinase (PI3K) [Refs 36, 37, 38] (Figure 1).

Roles of BMP4 in female reproductive physiology

The function of BMP4 in the endometrium

Endometrium is a regenerative organ that undergoes bleeding, proliferation and the secretory phase under the control of female hormones [Refs 39, 40]. Bone morphogenetic protein superfamily has been proven to regulate multiple endometrial functions, including proliferation, apoptosis, decidualization and immune cell infiltration [Ref. 41].

In bovine, BMP4 and its receptors were detected primarily in endometrial epithelial cells during the estrous cycle and early pregnancy, with higher protein levels observed during pregnancy. Exogenous BMP4 treatment in endometrial epithelial cells significantly suppressed proliferation without altering caspase-3/8 expression, while reducing prostaglandin E2 (PGE2) and PGF2α concentrations. Furthermore, the mRNA level of BMP4 was upregulated by pro-

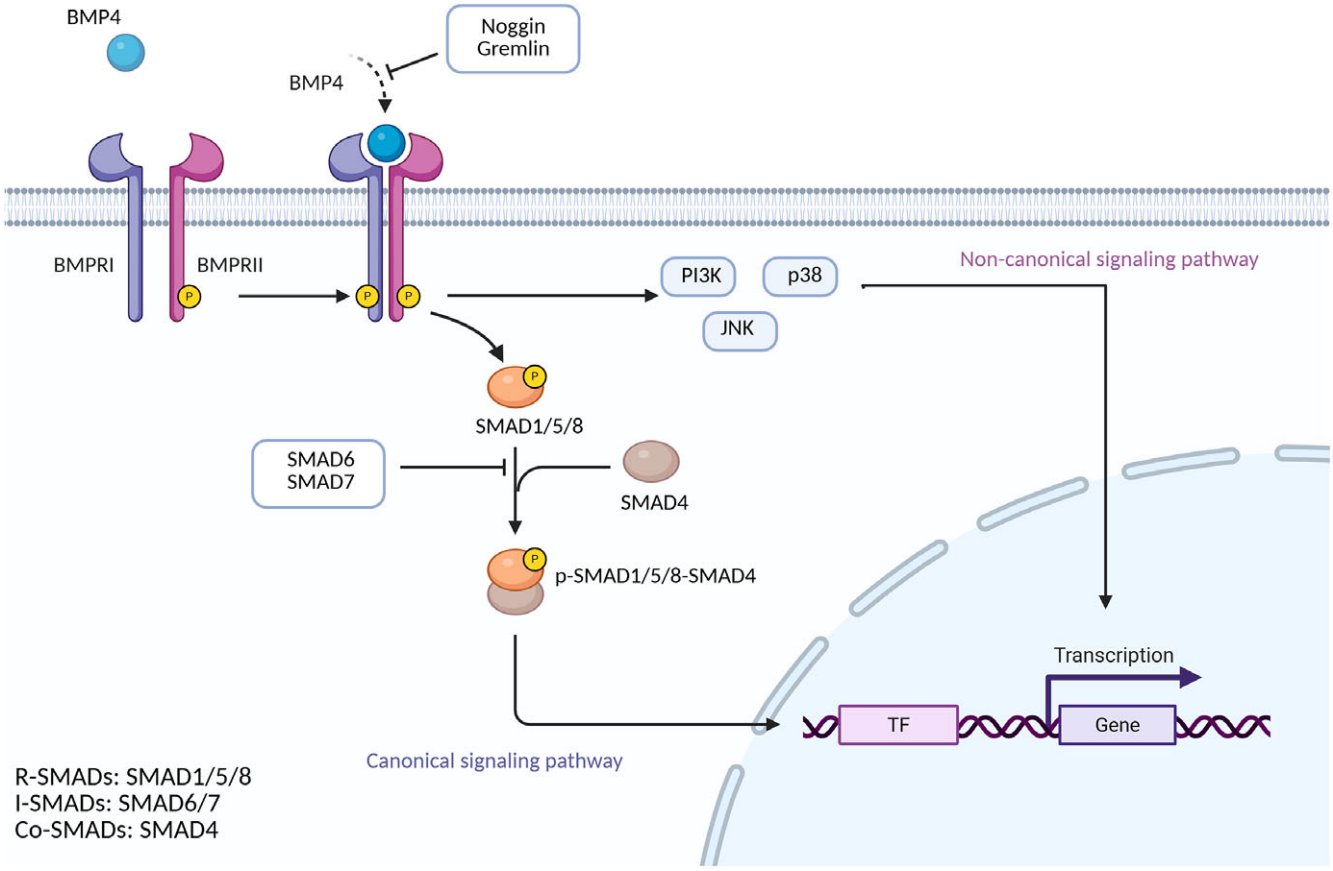


Figure 1. BMP4 cellular signaling pathway. BMP4 activates canonical SMAD-dependent and non-canonical signaling pathways through BMP receptors, ultimately regulating target gene transcription. Abbreviations: BMP4, bone morphogenetic protein 4; BMPRI, bone morphogenetic protein type I receptor; BMPRII, bone morphogenetic protein type II receptor; PI3K, phosphoinositide 3-kinase; JNK, c-Jun amino terminal kinase; p38, p38 mitogen-activated protein kinase; TF, transcription factor; p-, phosphorylated. The figure was created with BioRender.

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inflammatory cytokines, including tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), suggesting a potential regulatory link between immune signalling and endometrial BMP4 activity [Ref. 4]. Decidualization refers to the transformation of endometrial stromal cells (ESCs) into decidual stromal cells (DSCs), which is primarily driven by progesterone and intracellular cyclic adenosine monophosphate (cAMP) stimulation in the secretory phase. During this process, DSCs will secrete two specific protein markers, prolactin (PRL) and insulin-like growth factor binding protein 1 (IGFBP1), which will promote trophoblast invasion and support embryo development [Refs 42, 43]. Impaired decidualization may result in reproductive diseases such as RIF and RSA [Refs 44, 45]. BMP4 has been proven to regulate the process of decidualization [Refs 3, 46].

Our group's new study showed that BMP4 downregulation impaired decidualization by downregulating IGFBP1 and PRL, as well as the transcription factor forkhead box O1 (FOXO1). BMP4 impaired trophoblast migration and invasion by regulating FOXO1 in an in vitro co-culture model of stromal and trophoblast cells [Ref. 3]. Furthermore, O-fucosylation of BMP1 increased BMP4 level and activated the BMP/Smad signalling pathway to promote endometrial decidualization [Ref. 46].

Beyond its direct effect on decidualization, emerging evidence from a recent study suggests that BMP4 also influences endometrial immune tolerance. Another recent study of our group demonstrated that BMP4 inhibition will polarize THP-1 to M2-type macrophages through activating autophagy [Ref. 5]. M1-type macrophages primarily secrete pro-inflammatory cytokines, which impair trophoblast invasion and embryo implantation. But M2-type macrophages primarily secrete anti-inflammatory cytokines, which help build immune tolerance [Refs 47, 48]. However, current studies on their function in the endometrium remain limited. Moreover, while macrophages have been investigated, other immune cell populations in the decidua, such as natural killer cells (NK), T cells and other cell types, have not been fully explored. Hence, further studies are needed to comprehensively understand the immune regulatory functions of BMP4 at the maternal-foetal interface and its crosstalk with other members in the BMP superfamily.

The function of BMP4 in the ovary

Our group has previously summarized the expression of BMP4 in the ovary, as well as its roles in ovarian development and ovarian steroidogenesis in 2021 [Ref. 2]. This review pointed out that the BMP4 expression pattern in ovarian tissue exhibits spatiotemporal and species-specific characteristics and is closely associated with ovarian physiology. Specifically, BMP4 plays an important role in steroidogenesis and follicular development. Given the importance in this field, we present an updated synthesis of the latest findings to extend and complement our earlier review. Folliculogenesis is a highly coordinated process involving the growth and maturation of ovarian follicles from primordial to preovulatory follicles [Ref. 49]. During this process, granulosa cells (GCs) play a central role in supporting oocyte development, regulating follicular growth and producing steroid hormones that are essential for ovarian function [Ref. 50]. GCs are tightly regulated by multiple local growth factors, including BMP4. BMP4 enhances GCs proliferation while suppressing the synthesis of estradiol and progesterone induced by follicle-stimulating hormone (FSH) in bovine [Ref. 51], suggesting a complex role for BMP4 in the regulation of ovarian steroidogenesis. BMP4 suppresses the expression of steroidogenic acute regulatory protein (StAR), CYP11A1, as well as the NOTCH target gene hairy and enhancer of split 1 (HES1) in bovine GCs, highlighting the complex crosstalk between the NOTCH and BMP/Smad signalling pathways in regulating GCs function [Ref. 52]. In addition, BMP4 overexpression promoted GCs proliferation, whereas BMP4 knockdown increased apoptosis. BMP4 could induce Smad8 phosphorylation to regulate activin membrane binding inhibitor (BAMBI) expression, thereby promoting lipid synthesis in Wanxi White goose GCs [Ref. 53]. An earlier review pointed out the potential role of BMP4 in cumulus cell expansion [Ref. 2]; subsequent studies also provide support. BMP4 is expressed in cumulus cells, whose protein is localized in both the cytoplasm and nucleus in bovine. BMP4 knockdown increases apoptosis and inhibits proliferation by upregulating cysteine-aspartic acid protease 3 (Caspase-3) and bcl-2 associated x protein (BAX), while downregulating B-cell lymphoma 2 (Bcl-2) and cell cycle arrest at the G0/G1 phase [Ref. 54].

The function of BMP4 in ovarian steroidogenesis

The development and maturation of ovarian follicles are tightly regulated by FSH and luteinizing hormone (LH), whose secretion is governed by hypothalamic gonadotropin-releasing hormone (GnRH) [Refs 55, 56]. Moreover, the secretion of FSH and LH is regulated by ovarian-derived steroid hormones, activin and inhibin through feedback mechanisms [Refs 57, 58]. Our previous review has summarized the role of BMP4 in ovarian steroidogenesis. Overall, BMP4 could regulate FSH receptor (FSHR) expression in both theca and GCs, although these effects vary across species. In addition, BMP4 is also demonstrated to regulate the expression of oestrogen, progesterone, as well as anti-Müllerian hormone (AMH) [Ref. 2]. A new study found that BMP4 inhibited FSH- and IGF1-induced progesterone and oestrogen production in primary GCs isolated from bovine small and large follicles. Notably, BMP4 exerted a more pronounced inhibitory effect on oestrogen production in large follicles [Ref. 51]. This indicates BMP4 may exert a direct effect on ovarian steroidogenesis. In addition, BMP4 stimulates Noggin4 expression, and Noggin4 knockdown reduces the expression of the steroidogenic genes StAR and CYP11A1 in chicken GCs [Ref. 59]. This finding highlights a potential paracrine regulatory mechanism of BMP4-mediated ovarian steroidogenesis.

Beyond its well-established roles in regulating FSH, oestrogen and progesterone synthesis, recent five-year studies have highlighted that BMP4 could also modulate androgen synthesis, which was not fully addressed in previous reviews. BMP4 has been shown to negatively regulate androgen synthesis by suppressing CYP17A1 expression, thereby inhibiting LH-induced androgen production in bovine theca cells [Refs 60, 61]. And exogenous BMP4 treatment suppressed androgen synthesis in theca cells and promoted oestrogen production in GCs in a dehydroepiandrosterone (DHEA)-induced PCOS mouse model [Refs 62]. Our new study comfirmed that exogenous dihydrotestosterone (DHT) was found to induce BMP4 expression in a vitro human granulosa tumour cell line (KGN) in a dose-dependent manner. Overexpression of BMP4 mitigated the DHT-induced glycolysis and autophagy reduction, suggesting its protective role in ovary function [Ref. 63]. Moreover, intratesticular administration of BMP4 to rats did not affect testicular and epididymal weights, but serum testosterone levels in rats were downregulated in a dose-dependent manner. Smad1/4/5 was activated in BMP4-treated Leydig cells, and ERK1/2 and AMPL pathways were also activated, suggesting that BMP4 inhibits androgen synthesis by activating the above pathways [Ref. 64]. Evidence from other tissues also supports BMP4's role in androgen synthesis. In the H295R adrenocortical cell line, BMP4 reduced DHEA production by downregulating CYP17A1 via SMAD/1/5/8 activation

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[Ref. 65]. Additionally, mRNA expression levels of BMP4 and BMP type I receptor (Bmpr1a) were upregulated in intestinal stem cells of orchiectomized male mice, and supplementation with DHT suppressed BMP4 expression [Ref. 66]. These findings further suggest that BMP4 may broadly influence androgen synthesis, reinforcing its potential role in regulating ovarian and androgen production.

Roles of BMP4 in obesity

Obesity is a complex chronic metabolic disorder characterized not only by excessive AT accumulation and weight gain but also by persistent metabolic dysfunction, including insulin resistance and impaired glucose metabolism. In addition, obesity is associated with a state of chronic low-grade systemic inflammation, which is considered a key mechanism linking obesity to its metabolic and reproductive complications [Refs 56, 67] .

The function of BMP4 in adipogenesis

There are two main types of adipose tissue: WAT and BAT. WAT serves mainly as an energy storage in response to nutritional need. While BAT mediates non-shivering thermogenesis by uncoupling mitochondrial respiration from ATP production [Refs 68–71]. Adipogenesis, a process from MSCs to fully mature adipocytes, is divided into two main stages. During the first stage, MSCs commit to the adipogenic lineage under the control of critical transcription factors, especially peroxisome proliferator-activated receptor γ (PPARγ) and C/EBPα. The second stage is the terminal differentiation of the adipogenic lineage into fully mature adipocytes [Refs 72, 73, 74]. BMP4 plays a crucial role in directing MSCs toward the adipocyte lineage [Refs 6, 7]. But the role of BMP4 in inducing pre-adipocytes toward BAT or WAT remains controversial. One study demonstrated that BMP4 promotes white-to-brown adipocyte transition by increasing the expression of the BAT marker uncoupling protein 1 (UCP1) and decreasing the WAT marker transcription factor 21 (TCF21) in human subcutaneous adipose stem cells [Ref. 75]. BMP4 promotes pre-adipocytes toward beige or brown adipose phenotypes and increases PGC1α expression through activating PPARγ transcriptional activity. But this process can be inhibited by the BMP antagonist Gremlin 1 (GREM1) [Refs 7, 8]. Another study also demonstrated that BMP4 promotes the browning or beiging program by inducing UCP1 expression in mouse-derived C3H10T1/2 cells [Ref. 76]. In addition, BMP4, secreted by adipocyte cells, could activate M2 type macrophage and inhibit M1 type macrophage to induce beige adipocyte shift [Ref. 10]. Another study found that BMP4 increased the WAT marker (Resistin) but decreased the BAT marker UCP1, suggesting that BMP4 promotes a shift from a brown to a white-like adipocyte phenotype. In addition, BMP4 impaired BAT bioenergetics, including decreasing the mitochondrial number, maximal fatty acid oxidation capacity and tricarboxylic acid (TCA) cycle activity. This may be due to activating SMAD signalling pathway or suppressing lipolysis ability [Ref. 9]. The contradictory results may be due to differences in the origins of adipocytes across studies, highlighting the need for further research to clarify the mechanisms.

The function of BMP4 in insulin resistance and inflammation

Obesity is commonly characterized by chronic systemic inflammation. This inflammatory state contributes to metabolic dysregulation, including insulin resistance, and is associated with the development of various diseases such as cardiovascular disease and PCOS [Refs 77, 78]. A study pointed out that serum BMP4 concentrations positively correlated with adipocyte hypertrophy and whole-body insulin sensitivity [Ref. 9], suggesting a potential role for BMP4 in regulating insulin signalling. Another study also found that serum BMP4 levels increased with age in a type 2 diabetes animal model. This may be due to BMP4 promoting insulin resistance by activating PKC-θ, which in turn attenuates insulin signaling [Ref. 11]. In addition, elevated BMP4 levels in diabetic animals were found to inhibit glucose-stimulated insulin secretion through upregulation of calbindin 1 [Ref. 79]. Collectively, these studies indicate that BMP4 may represent an important modulator of insulin signalling.

Chronic low-grade inflammation is increasingly recognized as a hallmark of obesity. Emerging evidence suggests that BMP4 may participate in regulating obesity-associated inflammatory responses. Increased BMP4 expression has been reported in the myocardium and aorta of obese mice, where BMP4 was associated with elevated inflammatory cytokine levels, and BMP4 knockdown alleviated local inflammatory responses [Ref. 80]. These findings suggest that BMP4 may exert distinct effects on inflammatory pathways depending on the tissue context. Further studies are required to clarify the role of BMP4 in obesity associated inflammation and its contribution to obesity-related metabolic complications.

BMP4 may be a potential bridge between obesity and female fertility: Current evidence and further directions

Collectively, the above findings suggest that BMP4 plays a crucial role in female reproductive physiology, influencing ovarian steroidogenesis, follicle development, endometrial cell proliferation and apoptosis, decidualization process and immune tolerance at the maternal-foetal interface. In addition, stable commitment of MSCs to adipocyte lineage requires BMP4. BMP4 also regulates the shift from pre-adipocyte to WAT or BAT, as well as the shift from WAT to beige adipocytes. Moreover, BMP4 is also involved in regulating insulin resistance and inflammation (Figure 2).

Although the specific role of BMP4 in the obese female reproductive system remains unclear, a study reported significantly elevated serum BMP4 levels in obese women, suggesting that BMP4 may be involved in obesity-associated reproductive dysfunction [Ref. 81]. Serum BMP4 levels correlated with wrist circumference and high-density lipoprotein cholesterol (HDL-C) [Ref. 82]. In addition, BMP4 expression was also found to be increased in ovarian follicles, along with high lipid droplets in high-fat diet-induced obese mouse models [Ref. 83]. These observations suggest that BMP4 signalling may link obesity with reproductive functions. Nevertheless, there remains a lack of data on BMP4 expression in specific reproductive tissues of obese women, such as the endometrium and the ovary.

Previous studies have shown that BMP4 is a crucial regulator of decidualization. Given that obesity is associated with impaired decidualization in both mice and human ESCs [Ref. 84], altered BMP4 signalling may represent one potential mechanism underlying impaired endometrial receptivity and implantation in obesity. In addition, leptin, which is secreted by adipocytes, regulates the proliferation and apoptosis of endometrial epithelial cells. In addition, leptin has been implicated in the regulation of endometrial receptivity by upregulating the expression of β3-integrin [Refs 22, 25]. Interestingly, the percentage of M1 type macrophages (pro-inflammatory) is lower in obese women compared to healthy women, which suggests

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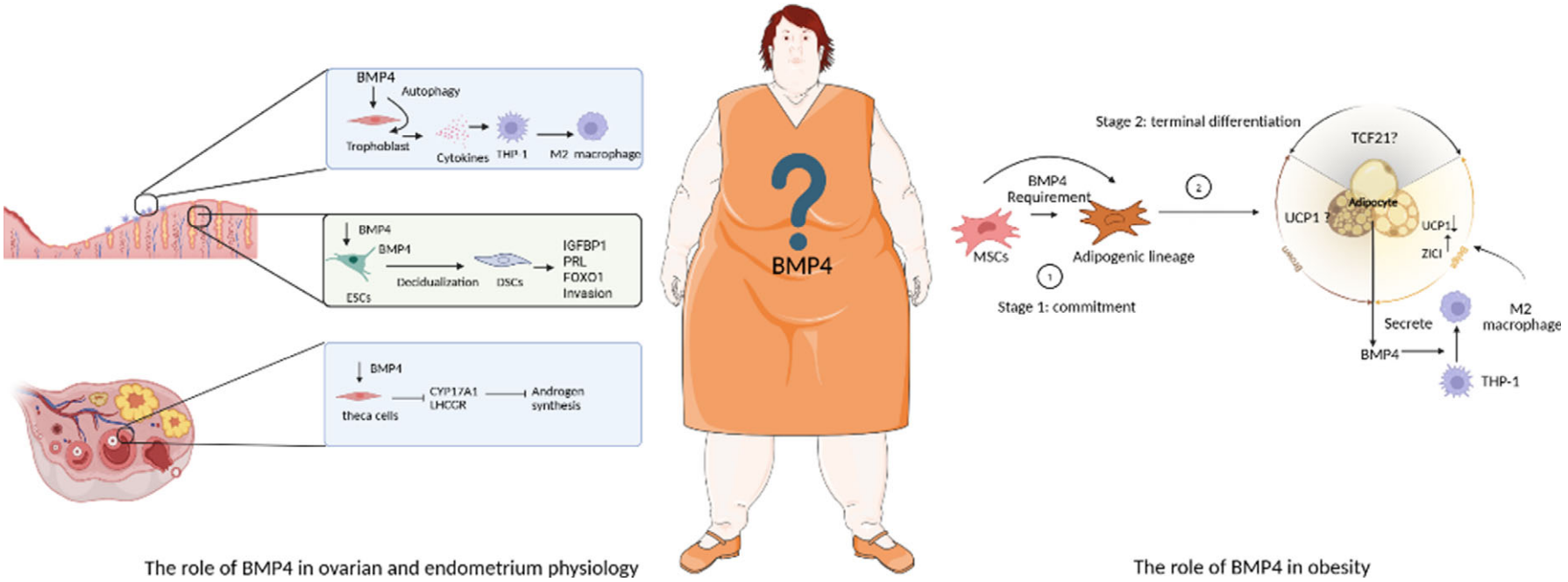


Figure 2. BMP4 as a potential molecular link between adipogenesis and female reproductive physiology. Schematic overview of BMP4 function in the endometrium, ovary, and adipose tissue, with a focus on decidualization, ovarian androgen synthesis, macrophage polarization, and adipogenic differentiation. Abbreviations: BMP4, bone morphogenetic protein 4; ESC, endometrial stromal cell; FOXO1, forkhead box O1; IGFBP1, insulin-like growth factor binding protein 1; PRL, prolactin; CYP17A1, cytochrome P450 family 17 subfamily A member 1; E2, estradiol; MSCs, mesenchymal stem cells; TCF21, transcription factor 21; UCP1, uncoupling protein 1; ZIC1, zinc finger protein of the cerebellum 1; THP-1, human monocytic leukemia cell line; M1/M2, macrophage phenotypes.

an existing protective mechanism [Ref. 85]. And our previous study found that BMP4 could promote macrophage polarization toward an anti-inflammatory M2 phenotype [Ref. 5]. Given the critical role of macrophage polarization in maintaining the endometrial immune microenvironment, these findings suggest BMP4 may act as a potential regulator of endometrial function in obese women. However, this hypothesis remains to be experimentally validated.

Furthermore, a study found that BMP4 deficiency in WAT increased oestrogen receptor α levels to prevent obesity and insulin resistance in high-fat diet-induced adult obese mice. Conversely, oestrogen depletion upregulated BMP4 expression to counteract age-related fat accumulation [Ref. 86]. This study indicates that BMP4 may influence ovarian hormone regulation in obese females, further supporting its potential role as a link between obesity and fertility. However, more studies are needed to clarify its impact on obese women.

Altered expression and functional implications of BMP4 in female reproductive disease

BMP4 is increasingly regarded as a critical regulator in female reproductive physiology, with dysregulation implicated in multiple reproductive disorders. Although we reviewed PCOS, RSA, infertility, premature ovarian insufficiency (POI), endometriosis and adenomyosis, only PCOS and RSA had studies directly exploring the role of BMP4 (Table 1).

BMP4 is involved in polycystic ovary syndrome (PCOS)

PCOS is a common female reproductive disorder that affects approximately 10%–30% of women worldwide [Ref. 94]. The commonly used clinical diagnostic criteria are still the Rotterdam criteria, which require that patients meet at least two of the following symptoms: 1) oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, 3) polycystic ovaries, and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome) [Ref. 95]. However, the exact mechanism of PCOS is still obscure. Current studies have investigated the role of BMP4 in PCOS using both human samples and androgen-induced PCOS animal models (Table 1).

In humans, BMP4 expression has been examined in peripheral blood or GCs by using ELISA assay, RT-PCR or immunohistochemistry. A study including 8 PCOS patients and 6 healthy controls found no significant difference in BMP4 mRNA expression in GCs between PCOS and control groups [Ref. 87]. In contrast, another study that involved 40 PCOS and 20 healthy controls found BMP4 mRNA expression downregulated in GCs of PCOS patients when compared to healthy controls [Ref. 90]. To date, only two studies have examined BMP4 expression in GCs from PCOS patients, and they reported differently. These discrepancies may be due to differences in ethnicity and the small sample sizes. Therefore, additional studies with larger sample sizes and a diverse population are needed. Circulating BMP4 levels have also been investigated in PCOS patients. The paper published in 2013 examined serum BMP4 levels in 20 PCOS patients and found that BMP4 expression was undetectable across all samples. This finding may be attributed to the lower detection limit of the ELISA assay used (31.2 pg/mL) [Ref. 88]. However, a recent 2025 paper compared serum BMP4 levels between 40 PCOS patients and 40 healthy controls. When stratified by BMI, BMP4 levels were significantly upregulated in normal-weight controls compared with normal-weight PCOS patients. However, no significant difference was observed between PCOS patients and healthy controls when BMI was not considered [Ref. 92]. Hence, these findings suggest that BMP4 may be more closely associated with metabolic status, such as obesity. In addition, circulating BMP4 levels appear to vary with androgen status. One study reported that serum BMP4 was upregulated in hyperandrogenic PCOS when compared with the non-hyperandrogenic PCOS group [Ref. 63].

Hyperandrogen-induced PCOS mouse models enable direct examination of ovarian tissues, which is difficult to achieve in human studies because of ethical constraints. Two studies each included 10 PCOS mouse models and 10 healthy control mouse models to investigate the ovarian BMP4 expression. However, the findings were inconsistent. One study reported decreased BMP4 mRNA and protein level in the PCOS mouse model ovary by using RT-PCR and western blot [Ref. 63]. Whereas another study observed increased BMP4 mRNA expression in the PCOS mouse model ovary by RT-PCR [Ref. 89]. Liu et al. found that the BMP4-Smad pathway could regulate ovarian steroidogenesis by inhibiting androgen synthesis in theca cells and promoting estrogen production [Ref. 62]. In addition, a 2024 study combined transcriptomic and DNA methylation analyses of ovarian GCs from four DHEA-induced PCOS-like mice and four control mice. BMP4 was identified as a hypomethylated and upregulated gene, suggesting that aberrant DNA hypomethylation may contribute to its increased expression in PCOS through an epigenetic mechanism [Ref. 91]. It is known that PCOS is always associated with obesity and insulin resistance [Ref. 96]. A recent study indicates that in a high-fat diet-induced mouse obese model, BMP4 expression is upregulated in ovarian follicles, along with higher levels of inflammatory cytokines, oxidative stress (ROS), DNA damage and lipid accumulation [Ref. 83].

BMP4 is Involved in recurrent spontaneous abortion (RSA)

RSA is defined as two or more consecutive miscarriages before 20 weeks of gestation with the same sexual partner. The incidence of RSA is difficult to estimate because the criteria of RSA are still somewhat controversial. Some women also conceal their history of abortion for social or cultural reasons [Ref. 97]. However, there are still several clinical studies with large samples which allow us to get some approximate idea of the incidence of miscarriages. In Europe, RSA affects about 1%–2% of couples, according to guidelines from the European Society for Human Reproduction and Embryology [Ref. 98]. Therefore, it is crucial to clarify the pathogenesis and treatment of RSA.

Although studies on BMP4 in RSA remain limited, accumulating evidence in recent years has highlighted its potential importance in RSA pathogenesis. Wei et al. reviewed the important role of the BMP family in the menstrual cycle and pregnancy [Ref. 41]. In our group's previous studies, BMP4 expression was found to be reduced in both decidual and villous tissues from RSA patients, highlighting its complex regulatory roles at the maternal–foetal interface. Specifically, decreased BMP4 impaired decidualization by modulating FOXO1 expression, suppressed trophoblast invasion partly via runt-related transcription factor 2 (RUNX2) and promoted macrophage M1 polarization through inhibition of autophagy [Refs 3, 5]. Furthermore, a case–control study analysing 70 RSA and 100 healthy controls in Iran reported that the AA genotype of BMP4 rs121912765 polymorphism was significantly enriched in RSA patients [Ref. 93]. A previous study has also found BMP4 to be associated with embryonic development, suggesting the importance of BMP4 in pregnancy. scRNA-seq analysis and

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Table 1. Summary of BMP4 expression and functional implications in PCOS and RSA

Author	Expression	Location	Sample numbers	Species	Methods	Function
PCOS						
Khalaf et al. [Ref. 87]	No difference	Granulosa cells	8 PCOS versus 6 healthy controls	Human	RT-PCR & immunohistochemistry	–
Houten et al. [Ref. 88]	No detected	Blood	20 PCOS	Human	ELISA assay	–
Tang et al. [Ref. 89]	Upregulated in PCOS	Ovary	10 PCOS versus 10 healthy controls	Hyperandrogen-induced PCOS mouse model	RT-PCR	CMKLR1 deficiency attenuates the DHT-induced increase in BMP4 activity, thereby partially relieving the suppression of progesterone production and ovulation
Wu et al. [Ref. 90]	Downregulated in PCOS	Grandulosa cells	40 PCOS versus 20 healthy controls	Human	RT-PCR	–
Liu et al. [Ref. 62]	Downregulated in PCOS	Ovary	10 PCOS versus 10 healthy controls	Hyperandrogen-induced PCOS mouse model	RT-PCR & western blot	1. BMP4 expression is suppressed by elevated androgens through activation of androgen receptors; 2. BMP4 regulates ovarian steroidogenesis by suppressing androgen synthesis in theca cells and promoting estrogen production in granulosa cells via SMAD signaling pathway
Gu et al. [Ref. 63]	Upregulated in hyperandrogenic PCOS when compared with non-hyperandrogenic PCOS group	Blood	8 PCOS versus Hyperandrogenic PCOS	Human	ELISA assay	1. DHT induces BMP4 expression in human granulosa cells line (KGN) dose-dependently; 2. BMP4 overexpression mitigates DHT-induced glycolysis and antophagy reduction
Cao et al. [Ref. 91]	Upregulated in PCOS	Grandulosa cells	4 PCOS versus 4 healthy controls	Hyperandrogen-induced PCOS mouse model	Methyl-RAD-seq & RNA-seq	BMP4 potentially regulated by aberrant DNA hypomethylation in PCOS
Bakar et al. [Ref. 92]	Upregulated in normal weight control when compared to normal weight PCOS group	Blood	40 PCOS versus 40 healthy controls	Human	ELISA assay	–
RSA						
Mazdapour et al. [Ref. 93]	The AA genotype of the BMP4 rs121912765 polymorphism was significantly enriched in RSA patients, whereas the AG genotype was more prevalent in normal controls	Blood	70 RSA versus 100 healthy controls	Human	Polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) assay	–
Huang et al. [Ref. 3]	Downregulated in RSA	Decidual tissue	13 RSA versus 12 healthy controls	Human	RT-PCR & western blot & immunohistochemistry	Knockdown BMP4 impairs decidualization, ageing, and trophoblast migration and invasion via FOXO1 regulation
Tang et al. [Ref. 5]	Downregulated in RSA	Villous tissue	10 RSA versus 22 healthy controls	Human	RT-PCR & western blot & immunohistochemistry	1. Knockdown BMP4 impairs trophoblast function partly due to RUNX2 expression; 2. Knockdown BMP4 promote M1 macrophage polarization by inhibiting autophagy, whereas overexpression drives M2 polarization via promoting autophagy

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spatiotemporal analysis of mouse extraembryonic ectoderm (ExE) revealed a steep increase in the expression level of Bmp4 at day 7 of embryonic development, when Bmp4 is present in the early neonatal mesoderm and has the highest level of expression in the extraembryonic mesoderm (ExM), amniotic membrane and urothelium. Furthermore, germline Bmp4-KO embryos exhibited developmental delay and had no urothelium visible, indicating impaired developmental competence [Ref. 99]. Although the role of BMP4 in RSA remains unclear, its importance in embryonic development and our current findings suggest that it plays a key role in pregnancy and warrants further investigation.

Summary

In this review, we summarize the role of BMP4 in female reproductive physiology, ovarian hormone synthesis, adipogenesis and pathogenesis of female reproductive diseases. The current research results showed that BMP4 regulates ovarian steroidogenesis, endometrial decidualization, trophoblast invasion and immune tolerance at the maternal-foetal interface. In addition, BMP4 is a key regulator of adipogenesis and of the shift from BAT to WAT. Aberrant BMP4 expression has been reported in PCOS and RSA, both in peripheral blood and diseased tissues. In addition, elevated BMP4 levels have also been observed in obese women and in the ovaries of obese mouse models. Considering that obesity may impair endometrial decidualization and BMP4 could modulate this process, BMP4 may serve as a potential mediator linking obesity and female fertility. However, despite these insights, whether BMP4 directly contributes to reproductive dysfunction in obese women remains unknown and requires further investigation. Moreover, while BMP4 has been studied in PCOS and RSA, its role in other reproductive disorders, such as endometriosis, adenomyosis and POI, remains underexplored, highlighting important directions for future research.

Availability of data and materials. No datasets were generated or analysed during the current study.

Author contribution. YZ and FD designed this review. YZ and JZ wrote the draft. GC and FD critically revised the manuscript. Finally, the manuscript was approved by all authors.

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References

1. **Hogan BL** (1996) Bone morphogenetic proteins in development. *Current Opinion in Genetics & Development* **6**(4), 432–438. https://doi.org/10.1016/S0959-437X(96)80064-5.
2. **Yang D**, **Yang X**, **Dai F**, **Wang Y**, **Yang Y**, **Hu M and Cheng Y** (2021) The role of bone morphogenetic protein 4 in ovarian function and diseases. *Reproductive Sciences* **28**(12), 3316–3330. https://doi.org/10.1007/s43032-021-00600-8.
3. **Huang Y**, **Dai F**, **Chen L**, **Li Z**, **Liu H and Cheng Y** (2024) BMP4 in human endometrial stromal cells can affect decidualization by regulating FOXO1 expression. *Endocrinology* **165**(6). https://doi.org/10.1210/endocr/bqae049.
4. **Koizumi Y**, **Hayashi KG and Sakumoto R** (2023) Possible roles of bone morphogenetic protein 4 in regulating endometrial function in cows. *Animal Science Journal* **94**(1), e13866. https://doi.org/10.1111/asj.13866.
5. **Tang L**, **Dai F**, **Zhang Y**, **Wang R**, **Tan W**, **Gu R**, **Chen L**, **Wang L**, **Liu H**, **Cheng Y and Xia L** (2025) Deletion of BMP4 impairs trophoblast function and decidual macrophage polarization via autophagy leading to recurrent spontaneous abortion. *International Immunopharmacology* **147**, 114015. https://doi.org/10.1016/j.intimp.2025.114015.
6. **Bowers RR**, **Kim JW**, **Otto TC and Lane MD** (2006) Stable stem cell commitment to the adipocyte lineage by inhibition of DNA methylation: role of the BMP-4 gene. *Proceedings of the National Academy of Sciences of the United States of America* **103**(35), 13022–13027. https://doi.org/10.1073/pnas.0605789103.
7. **Huang H**, **Song TJ**, **Li X**, **Hu L**, **He Q**, **Liu M**, **Lane MD and Tang QQ** (2009) BMP signaling pathway is required for commitment of C3H10T1/2 pluripotent stem cells to the adipocyte lineage. *Proceedings of the National Academy of Sciences of the United States of America* **106**(31), 12670–12675. https://doi.org/10.1073/pnas.0906266106.
8. **Gustafson B**, **Hammarstedt A**, **Hedjazifar S**, **Hoffmann JM**, **Svensson PA**, **Grimsby J**, **Rondinone C and Smith U** (2015) BMP4 and BMP antagonists regulate human white and beige adipogenesis. *Diabetes* **64**(5), 1670–1681. https://doi.org/10.2337/db14-1127.
9. **Modica S**, **Straub LG**, **Balaz M**, **Sun W**, **Varga L**, **Stefanicka P**, **Profant M**, **Simon E**, **Neubauer H**, **Ukropcova B**, **Ukropec J and Wolfrum C** (2016) Bmp4 promotes a Brown to white-like adipocyte shift. *Cell Reports* **16**(8), 2243–2258. https://doi.org/10.1016/j.celrep.2016.07.048.
10. **Qian SW**, **Tang Y**, **Li X**, **Liu Y**, **Zhang YY**, **Huang HY**, **Xue RD**, **Yu HY**, **Guo L**, **Gao HD**, **Liu Y**, **Sun X**, **Li YM**, **Jia WP and Tang QQ** (2013) BMP4-mediated brown fat-like changes in white adipose tissue alter glucose and energy homeostasis. *Proceedings of the National Academy of Sciences of the United States of America* **110**(9), E798–E807. https://doi.org/10.1073/pnas.1215236110.
11. **Chattopadhyay T**, **Singh RR**, **Gupta S and Surolia A** (2017) Bone morphogenetic protein-7 (BMP-7) augments insulin sensitivity in mice with type II diabetes mellitus by potentiating PI3K/AKT pathway. *BioFactors* **43**(2), 195–209. https://doi.org/10.1002/biof.1334.
12. **Rubino F**, **Cummings DE**, **Eckel RH**, **Cohen RV**, **Wilding JPH**, **Brown WA**, **Stanford FC**, **Batterham RL**, **Farooqi IS**, **Farpour-Lambert NJ**, **le Roux CW**, **Sattar N**, **Baur LA**, **Morrison KM**, **Misra A**, **Kadowaki T**, **Tham KW**, **Sumithran P**, **Garvey WT**, **Kirwan JP**, **Fernández-Real JM**, **Corkey BE**, **Toplak H**, **Kokkinos A**, **Kushner RF**, **Branca F**, **Valabhji J**, **Blüher M**, **Bornstein SR**, **Grill HJ**, **Ravussin E**, **Gregg E**, **al Busaidi NB**, **Alfaris NF**, **al Ozairi E**, **Carlsson LMS**, **Clément K**, **Després JP**, **Dixon JB**, **Galea G**, **Kaplan LM**, **Laferrère B**, **Laville M**, **Lim S**, **Luna Fuentes JR**, **Mooney VM**, **Nadglowski J, Jr**, **Urudinachi A**, **Olszanecka-Glinianowicz M**, **Pan A**, **Pattou F**, **Schauer PR**, **Tschöp MH**, **van der Merwe MT**, **Vettor R and Mingrone G** (2025) Definition and diagnostic criteria of clinical obesity. *The Lancet Diabetes and Endocrinology* **13**(3), 221–262. https://doi.org/10.1016/S2213-8587(24)00316-4.
13. **Cooper AJ**, **Gupta SR**, **Moustafa AF and Chao AM** (2021) Sex/gender differences in obesity prevalence, comorbidities, and treatment. *Current Obesity Reports* **10**(4), 458–466. https://doi.org/10.1007/s13679-021-00453-x.
14. **Ameratunga D**, **Gebeh A and Amoako A** (2023) Obesity and male infertility. *Best Practice & Research Clinical Obstetrics & Gynaecology* **90**, 102393. https://doi.org/10.1016/j.bpobgyn.2023.102393.
15. **Cena H**, **Chiovato L and Nappi RE** (2020) Obesity, polycystic ovary syndrome, and infertility: A new avenue for GLP-1 receptor agonists. *The Journal of Clinical Endocrinology and Metabolism* **105**(8), e2695–e2709. https://doi.org/10.1210/clinem/dgaa285.
16. **Ennab F and Atiomo W** (2023) Obesity and female infertility. *Best Practice & Research. Clinical Obstetrics & Gynaecology* **89**, 102336. https://doi.org/10.1016/j.bpobgyn.2023.102336.
17. **Wang RQ**, **Deng ZM**, **Chen GT**, **Dai FF and Xia LB** (2025) Obesity and recurrent spontaneous abortion: The crucial role of weight management in pregnancy. *Reproductive Biology and Endocrinology* **23**(1), 10. https://doi.org/10.1186/s12958-024-01326-3.
18. **Yu S**, **Lian RC**, **Chen C**, **Chen X**, **Xu J**, **Zeng Y and Li YY** (2023) Impact of body mass index on peripheral and uterine immune status in the window of

implantation in patients with recurrent reproductive failure. *Human Fertility* **26**(5), 1322–1333. https://doi.org/10.1080/14647273.2023.2189024.
19. **Sermondade N**, **Huberlant S**, **Bourhis-Lefebvre V**, **Arbo E**, **Gallot V**, **Colombani M and Fréour T** (2019) Female obesity is negatively associated with live birth rate following IVF: A systematic review and meta-analysis. *Human Reproduction Update* **25**(4), 439–451. https://doi.org/10.1093/humupd/dmz011.
20. **Broughton DE and Moley KH** (2017) Obesity and female infertility: Potential mediators of obesity's impact. *Fertility and Sterility* **107**(4), 840–847. https://doi.org/10.1016/j.fertnstert.2017.01.017.
21. **Chen Z**, **E Y**, **Xiong J**, **Li W**, **Chen X**, **Li N**, **Long J**, **Tong C**, **He J**, **Li F**, **Zhang C**, **Wang Y and Gao R** (2023) Dysregulated glycolysis underpins high-fat-associated endometrial decidualization impairment during early pregnancy in mice. *Biochimica et Biophysica Acta - Molecular Basis of Disease* **1869**(4), 166659. https://doi.org/10.1016/j.bbadis.2023.166659.
22. **Gonzalez RR and Leavis P** (2001) Leptin upregulates beta3-integrin expression and interleukin-1beta, upregulates leptin and leptin receptor expression in human endometrial epithelial cell cultures. *Endocrine* **16**(1), 21–28. https://doi.org/10.1385/ENDO:16:1:21.
23. **Bragdon B**, **Moseychuk O**, **Saldanha S**, **King D**, **Julian J and Nohe A** (2011) Bone morphogenetic proteins: a critical review. *Cellular Signalling* **23**(4). https://doi.org/10.1016/j.cellsig.2010.10.003.
24. **Li M**, **Chen Q**, **Sun G**, **Shi X**, **Zhao Q**, **Zhang C**, **Zhou J and Qin N** (2010) Characterization and expression of bone morphogenetic protein 4 gene in postnatal pigs. *Molecular Biology Reports* **37**(5), 2369–2377. https://doi.org/10.1007/s11033-009-9743-8.
25. **Tabas JA**, **Hahn GV**, **Cohen RB**, **Seaunez HN**, **Modi WS**, **Wozney JM**, **Zasloff M and Kaplan FS** (1993) Chromosomal assignment of the human gene for bone morphogenetic protein 4. *Clinical Orthopaedics and Related Research* (293), 310–316. https://doi.org/10.1097/00003086-199308000-00042.
26. **van den Wijngaard A**, **Weghuis DO**, **Boersma CJC**, **van Zoelen EJJ**, **van Kessel AG and Olijve W** (1995) Fine mapping of the human bone morphogenetic protein-4 gene (BMP4) to chromosome 14q22-q23 by in situ hybridization. *Genomics* **27**(3), 559–560. https://doi.org/10.1006/geno.1995.1096.
27. **Cui Y**, **Jean F**, **Thomas G and Christian JL** (1998) BMP-4 is proteolytically activated by furin and/or PC6 during vertebrate embryonic development. *The EMBO Journal* **17**(16), 4735–4743. https://doi.org/10.1093/emboj/17.16.4735.
28. **Miljkovic ND**, **Cooper GM and Marra KG** (2008) Chondrogenesis, bone morphogenetic protein-4 and mesenchymal stem cells. *Osteoarthritis and Cartilage* **16**(10), 1121–1130. https://doi.org/10.1016/j.joca.2008.03.003.
29. **Derynck R and Zhang YE** (2003) Smad-dependent and Smad-independent pathways in TGF-beta family signalling. *Nature* **425**(6958), 577–584. https://doi.org/10.1038/nature02006.
30. **Gomez-Puerto MC**, **Iyengar PV**, **García de Vinuesa A**, **ten Dijke P and Sanchez-Duffhues G** (2019) Bone morphogenetic protein receptor signal transduction in human disease. *The Journal of Pathology* **247**(1), 9–20. https://doi.org/10.1002/path.5170.
31. **Dexheimer V**, **Gabler J**, **Bomans K**, **Sims T**, **Omlor G and Richter W** (2016) Differential expression of TGF-β superfamily members and role of Smad1/5/9-signalling in chondral versus endochondral chondrocyte differentiation. *Scientific Reports* **6**(1), 36655. https://doi.org/10.1038/srep36655.
32. **Itoh S**, **Itoh F**, **Goumans MJ and ten Dijke P** (2000) Signaling of transforming growth factor-β family members through Smad proteins. *European Journal of Biochemistry* **267**(24), 6954–6967. https://doi.org/10.1046/j.1432-1327.2000.01828.x.
33. **Lawrence DA** (2002) Deficient R-smad/smad4 complex formation in fibroblasts growth-stimulated by TGF-beta 1. *International Journal of Oncology* **20**(4), 803–806.
34. **Li W**, **Li W**, **Zou L**, **Ji S**, **Li C**, **Liu K**, **Zhang G**, **Sun Q**, **Xiao F and Chen D** (2017) Membrane targeting of inhibitory Smads through palmitoylation controls TGF-β/BMP signaling. *Proceedings of the National Academy of Sciences of the United States of America* **114**(50), 13206–13211. https://doi.org/10.1073/pnas.1710540114.
35. **Yan X**, **Liao H**, **Cheng M**, **Shi X**, **Lin X**, **Feng XH and Chen YG** (2016) Smad7 protein interacts with receptor-regulated Smads (R-Smads) to inhibit transforming growth factor-β (TGF-β)/Smad Signaling. *The Journal of Biological Chemistry* **291**(1), 382–392. https://doi.org/10.1074/jbc.M115.694281.
36. **Imran KM**, **Rahman N**, **Yoon D**, **Jeon M**, **Lee BT and Kim YS** (2017) Cryptotanshinone promotes commitment to the brown adipocyte lineage and mitochondrial biogenesis in C3H10T1/2 mesenchymal stem cells via AMPK and p38-MAPK signaling. *Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids* **1862**(10), 1110–1120. https://doi.org/10.1016/j.bbalip.2017.08.001.
37. **Jeffery TK**, **Upton PD**, **Trembath RC and Morrell NW** (2005) BMP4 inhibits proliferation and promotes myocyte differentiation of lung fibroblasts via Smad1 and JNK pathways. *American Journal of Physiology. Lung Cellular and Molecular Physiology* **288**(2), L370–L378. https://doi.org/10.1152/ajplung.00242.2004.
38. **Lee MY**, **Lim HW**, **Lee SH and Han HJ** (2009) Smad, PI3K/Akt, and Wnt-dependent signaling pathways are involved in BMP-4-induced ESC self-renewal. *Stem Cells* **27**(8), 1858–1868. https://doi.org/10.1002/stem.124.
39. **Critchley HOD**, **Maybin JA**, **Armstrong GM and Williams ARW** (2020) Physiology of the endometrium and regulation of menstruation. *Physiological Reviews* **100**(3), 1149–1179. https://doi.org/10.1152/physrev.00031.2019.
40. **Murphy AR**, **Campo H and Kim JJ** (2022) Strategies for modelling endometrial diseases. *Nature Reviews Endocrinology* **18**(12), 727–743. https://doi.org/10.1038/s41574-022-00725-z.
41. **Wei D**, **Su Y**, **Leung PCK**, **Li Y and Chen ZJ** (2024) Roles of bone morphogenetic proteins in endometrial remodeling during the human menstrual cycle and pregnancy. *Human Reproduction Update* **30**(2), 215–237. https://doi.org/10.1093/humupd/dmad031.
42. **Gellersen B and Brosens JJ** (2014) Cyclic decidualization of the human endometrium in reproductive health and failure. *Endocrine Reviews* **35**(6), 851–905. https://doi.org/10.1210/er.2014-1045.
43. **Tong J**, **Lv S**, **Yang J**, **Li H**, **Li W and Zhang C** (2022) Decidualization and related pregnancy complications. *Maternal-Fetal Medicine* **4**(1), 24–35. https://doi.org/10.1097/FM9.0000000000000135.
44. **Tang L**, **Xu XH**, **Xu S**, **Liu Z**, **He Q**, **Li W**, **Sun J**, **Shuai W**, **Mao J**, **Zhao JY and Jin L** (2023) Dysregulated Gln-Glu-α-ketoglutarate axis impairs maternal decidualization and increases the risk of recurrent spontaneous miscarriage. *Cell Reports Medicine* **4**(5), 101026. https://doi.org/10.1016/j.xcrm.2023.101026.
45. **Zhang H**, **Kong L**, **Cao Z**, **Zhu Y**, **Jiang Y**, **Wang X**, **Jiang R**, **Liu Y**, **Zhou J**, **Kang Y**, **Zhen X**, **Kong N**, **Wu M**, **Yan G and Sun H** (2024) EHD1 impaired decidualization of endometrial stromal cells in recurrent implantation failure: Role of SENP1 in modulating progesterone receptor signalling. *Biology of Reproduction* **110**(3), 536–547. https://doi.org/10.1093/biolre/ioad161.
46. **Yang Y**, **Liang J**, **Chen S**, **Zhang A**, **Li Y**, **Liu S and Yan Q** (2023) O-Fucosylation of BMP1 promotes endometrial decidualization by activating BMP/Smad signaling pathway. *Biology of Reproduction* **109**(2), 172–183. https://doi.org/10.1093/biolre/ioad060.
47. **Zhao QY**, **Li QH**, **Fu YY**, **Ren CE**, **Jiang AF and Meng YH** (2022) Decidual macrophages in recurrent spontaneous abortion. *Frontiers in Immunology* **13**, 994888. https://doi.org/10.3389/fimmu.2022.994888.
48. **Wang LL**, **Li ZH**, **Wang H**, **Kwak-Kim J and Liao AH** (2022) Cutting edge: The regulatory mechanisms of macrophage polarization and function during pregnancy. *Journal of Reproductive Immunology* **151**, 103627. https://doi.org/10.1016/j.jri.2022.103627.
49. **Ezz MA and Balboula AZ** (2026) Molecular mechanisms of folliculogenesis and oogenesis. *Syst Biol Reprod Med* **72**(1), 211–240. https://doi.org/10.1080/19396368.2026.2631558.
50. **Wang H** (2025) The role of granulosa cells in oocyte development and aging: Mechanisms and therapeutic opportunities. *Seminars in Cell & Developmental Biology* **171**, 103614. https://doi.org/10.1016/j.semcdb.2025.103614.
51. **Spicer LJ**, **Schutz LF and Aad PY** (2021) Effects of bone morphogenetic protein 4, gremlin, and connective tissue growth factor on estradiol and progesterone production by bovine granulosa cells. *Journal of Animal Science* **99**(11). https://doi.org/10.1093/jas/skab318.
52. **Li Y**, **Jing J**, **Dang W**, **Jia K**, **Guo X**, **Kebreab E**, **Lyu L and Zhao J** (2022) Cross-talk between NOTCH2 and BMP4/SMAD signaling pathways in bovine follicular granulosa cells. *Theriogenology* **187**, 74–81. https://doi.org/10.1016/j.theriogenology.2022.04.016.
53. **Wei C**, **Chen X**, **Peng J**, **Yu S**, **Chang P**, **Jin K and Geng Z** (2023) BMP4/SMAD8 signaling pathway regulated granular cell proliferation to promote

follicle development in Wanxi white goose. *Poultry Science* **102**(1), 102282. https://doi.org/10.1016/j.psj.2022.102282.

54. **Tian YQ, Li XL, Wang WJ, Hao HS, Zou HY, Pang YW, Zhao XM, Zhu HB and du WH** (2022) Knockdown of bone morphogenetic protein 4 gene induces apoptosis and inhibits proliferation of bovine cumulus cells. *Theriogenology* **188**, 28–36. https://doi.org/10.1016/j.theriogenology.2022.05.015.
55. **Conn PM and Crowley WF** (1994) Gonadotropin-releasing hormone and its analogs. *Annual Review of Medicine* **45**(1), 391–405. https://doi.org/10.1146/annurev.med.45.1.391.
56. **Kaiser UB, Jakubowiak A, Steinberger A and Chin WW** (1997) Differential effects of gonadotropin-releasing hormone (GnRH) pulse frequency on gonadotropin subunit and GnRH receptor messenger ribonucleic acid levels in vitro. *Endocrinology* **138**(3), 1224–1231. https://doi.org/10.1210/endo.138.3.4968.
57. **Ling N, Ying SY, Ueno N, Shimasaki S, Esch F, Hotta M and Guillemin R** (1986) A homodimer of the beta-subunits of inhibin a stimulates the secretion of pituitary follicle stimulating hormone. *Biochemical and Biophysical Research Communications* **138**(3), 1129–1137. https://doi.org/10.1016/S0006-291X(86)80400-4.
58. **Santoro N, Filicori M and Crowley WF** (1986) Hypogonadotropic disorders in men and women: Diagnosis and therapy with pulsatile gonadotropin-releasing hormone. *Endocrine Reviews* **7**(1), 11–23. https://doi.org/10.1210/edrv-7-1-11.
59. **Gong Y, Li D, Sun Y, Kang L and Jiang Y** (2023) Expression and regulation of Noggin4 gene in chicken ovarian follicles and its role in the proliferation and differentiation of granulosa cells. *Theriogenology* **212**, 83–90. https://doi.org/10.1016/j.theriogenology.2023.09.007.
60. **Glister C, Regan SL, Samir M and Knight PG** (2019) Gremlin, noggin, chordin and follistatin differentially modulate BMP-induced suppression of androgen secretion by bovine ovarian theca cells. *Journal of Molecular Endocrinology* **62**(1), 15–25.
61. **Glister C, Satchell L and Knight PG** (2010) Changes in expression of bone morphogenetic proteins (BMPs), their receptors and inhibin co-receptor betaglycan during bovine antral follicle development: Inhibin can antagonize the suppressive effect of BMPs on thecal androgen production. *Reproduction* **140**(5), 699–712. https://doi.org/10.1530/REP-10-0216.
62. **Liu Y, du SY, Ding M, Dou X, Zhang FF, Wu ZY, Qian SW, Zhang W, Tang QQ and Xu CJ** (2017) The BMP4-Smad signaling pathway regulates hyperandrogenism development in a female mouse model. *The Journal of Biological Chemistry* **292**(28), 11740–11750. https://doi.org/10.1074/jbc.M117.781369.
63. **Gu R, Dai F, Xiang C, Chen J, Yang D, Tan W, Wang Z, Liu H and Cheng Y** (2023) BMP4 participates in the pathogenesis of PCOS by regulating glucose metabolism and autophagy in granulosa cells under hyperandrogenic environment. *The Journal of Steroid Biochemistry and Molecular Biology* **235**, 106410. https://doi.org/10.1016/j.jsbmb.2023.106410.
64. **Li X, Fang Y, Chen L, Quan H, Wang Y and Ge RS** (2022) Bone morphogenetic protein 4 inhibits rat stem/progenitor Leydig cell development and regeneration via SMAD-dependent and SMAD-independent signaling. *Cell Death & Disease* **13**(12), 1039. https://doi.org/10.1038/s41419-022-05471-8.
65. **Rege J, Nishimoto HK, Nishimoto K, Rodgers RJ, Auchus RJ and Rainey WE** (2015) Bone morphogenetic Protein-4 (BMP4): A paracrine regulator of human adrenal C19 steroid synthesis. *Endocrinology* **156**(7), 2530–2540. https://doi.org/10.1210/en.2014-1942.
66. **Yu X, Li S, Xu Y, Zhang Y, Ma W, Liang C, Lu H, Ji Y, Liu C, Chen D and Li J** (2023) Androgen maintains intestinal homeostasis by inhibiting BMP Signaling via intestinal stromal cells. *Stem Cell Reports* **18**(1), 410. https://doi.org/10.1016/j.stemcr.2022.11.022.
67. **Saltiel AR and Olefsky JM** (2017) Inflammatory mechanisms linking obesity and metabolic disease. *The Journal of Clinical Investigation* **127**(1), 1–4. https://doi.org/10.1172/JCI92035.
68. **Altinova AE** (2022) Beige adipocyte as the flame of white adipose tissue: Regulation of Browning and Impact of obesity. *The Journal of Clinical Endocrinology and Metabolism* **107**(5), e1778–e1788. https://doi.org/10.1210/clinem/dgab921.
69. **Aquila H, Link TA and Klingenberg M** (1985) The uncoupling protein from brown fat mitochondria is related to the mitochondrial ADP/ATP carrier. Analysis of sequence homologies and of folding of the protein in the membrane. *The EMBO Journal* **4**(9), 2369–2376. https://doi.org/10.1002/j.1460-2075.1985.tb03941.x.
70. **Reyes-Farias M, Fos-Domenech J, Serra D, Herrero L and Sánchez-Infantes D** (2021) White adipose tissue dysfunction in obesity and aging. *Biochemical Pharmacology* **192**, 114723. https://doi.org/10.1016/j.bcp.2021.114723.
71. **van Marken Lichtenbelt W** (2012) Brown adipose tissue and the regulation of nonshivering thermogenesis. *Current Opinion in Clinical Nutrition and Metabolic Care* **15**(6), 547–552. https://doi.org/10.1097/MCO.0b013e3283599184.
72. **Al Haj G, Rey F, Giallongo T, Colli M, Marzani B, Giuliani G, Gorio A, Zuccotti GV, Di Giulio AM and Carelli S** (2020) A new selective PPARγ modulator inhibits triglycerides accumulation during murine adipocytes' and human adipose-derived mesenchymal stem cells differentiation. *International Journal of Molecular Sciences* **21**(12). https://doi.org/10.3390/ijms21124415.
73. **Lai F, Wang J, Tang H, Bian X, Lu K, He G, Huang P, Liu J, Zhou M, Liu J, Tao X and Tang KL** (2021) Adipogenic differentiation was inhibited by downregulation of PPARγ signaling pathway in aging tendon stem/progenitor cells. *Journal of Orthopaedic Surgery and Research* **16**(1), 614. https://doi.org/10.1186/s13018-021-02720-y.
74. **Tang QQ and Lane MD** (2012) Adipogenesis: from stem cell to adipocyte. *Annual Review of Biochemistry* **81**(1), 715–736. https://doi.org/10.1146/annurev-biochem-052110-115718.
75. **Elsen M, Raschke S, Tennagels N, Schwahn U, Jelenik T, Roden M, Romacho T and Eckel J** (2014) BMP4 and BMP7 induce the white-to-brown transition of primary human adipose stem cells. *American Journal of Physiology. Cell Physiology* **306**(5), C431–C440. https://doi.org/10.1152/ajpcell.00290.2013.
76. **Xue R, Wan Y, Zhang S, Zhang Q, Ye H and Li Y** (2014) Role of bone morphogenetic protein 4 in the differentiation of brown fat-like adipocytes. *American Journal of Physiology. Endocrinology and Metabolism* **306**(4), E363–E372. https://doi.org/10.1152/ajpendo.00119.2013.
77. **Piche ME, Tchernof A and Despres JP** (2020) Obesity phenotypes, diabetes, and cardiovascular diseases. *Circulation Research* **126**(11), 1477–1500. https://doi.org/10.1161/CIRCRESAHA.120.316101.
78. **Marinelli S, Napoletano G, Straccamore M and Basile G** (2022) *Female obesity and infertility: outcomes and regulatory guidance. Acta Biomed* **93**(4), e2022278.
79. **Christensen GL, Jacobsen MLB, Wendt A, Mollet IG, Friberg J, Frederiksen KS, Meyer M, Bruun C, Eliasson L and Billestrup N** (2015) Bone morphogenetic protein 4 inhibits insulin secretion from rodent beta cells through regulation of calbindin1 expression and reduced voltage-dependent calcium currents. *Diabetologia* **58**(6), 1282–1290. https://doi.org/10.1007/s00125-015-3568-x.
80. **Wu T, Chen L, Shen Q, Wang L and Zong GJ** (2022) Role of bone morphogenetic protein 4 in the inflammation of the myocardium and vascular tissue of obese mice. *Journal of Cardiovascular Pharmacology* **79**(6), 791–798. https://doi.org/10.1097/FJC.0000000000001245.
81. **Yarsilikal Guleroglu F, Selvi E, Turan Bakirci I, Bafalı O, Argun Atalmis H, Yasti Dayan M, Balkan Ozmen A, Yurtcu N, Seker Atas B, Ozdemir Anayurt E and Cetin A** (2023) Clinical value of serum BMP-4, BMP-2, GDF-15, MMP-9, GP39 levels in pregnant women with obesity and the related comorbidities diabetes mellitus and gestational hypertension. *Zeitschrift für Geburtshilfe und Neonatologie* **227**(1), 42–50. https://doi.org/10.1055/a-1937-1155.
82. **Son JW, Kim MK, Park YM, Baek KH, Yoo SJ, Song KH, Son HS, Yoon KH, Lee WC, Cha BY, Son HY and Kwon HS** (2011) Association of serum bone morphogenetic protein 4 levels with obesity and metabolic syndrome in non-diabetic individuals. *Endocrine Journal* **58**(1), 39–46. https://doi.org/10.1507/endocrj.K10E-248.
83. **Wang L, Chen Y, Wei J, Guo F, Li L, Han Z, Wang Z, Zhu H, Zhang X, Li Z and Dai X** (2022) Administration of nicotinamide mononucleotide improves oocyte quality of obese mice. *Cell Proliferation* **55**(11), e13303. https://doi.org/10.1111/cpr.13303.
84. **Rhee JS, Saben JL, Mayer AL, Schulte MB, Asghar Z, Stephens C, Chi MMY and Moley KH** (2016) Diet-induced obesity impairs endometrial stromal cell decidualization: A potential role for impaired autophagy.

https://doi.org/10.1017/erm.2026.10068 Published online by Cambridge University Press

Human Reproduction **31**(6), 1315–1326. https://doi.org/10.1093/humrep/dew048.

85. **Laskewitz A, van Benthem KL, Kieffer TEC, Faas MM, Verkaik-Schakel RN, Plösch T, Scherjon SA and Prins JR** (2019) The influence of maternal obesity on macrophage subsets in the human decidua. *Cellular Immunology* **336**, 75–82. https://doi.org/10.1016/j.cellimm.2019.01.002.
86. **Qian SW, Liu Y, Wang J, Nie JC, Wu MY, Tang Y, Zhao YX, Li X, Huang HY, Guo L, Liu XS, Xu CJ and Tang QQ** (2016) BMP4 cross-talks with Estrogen/ERα signaling to regulate adiposity and glucose metabolism in females. *eBioMedicine* **11**, 91–100. https://doi.org/10.1016/j.ebiom.2016.07.034.
87. **Khalaf M, Morera J, Bourret A, Reznik Y, Denoual C, Herlicoviez M, Mittre H and Benhaim A** (2013) BMP system expression in GCs from polycystic ovary syndrome women and the in vitro effects of BMP4, BMP6, and BMP7 on GC steroidogenesis. *European Journal of Endocrinology* **168**(3), 437–444. https://doi.org/10.1530/EJE-12-0891.
88. **van Houten EL, Laven JSE, Louwers YV, McLuskey A, Themmen APN and Visser JA** (2013) Bone morphogenetic proteins and the polycystic ovary syndrome. *Journal of Ovarian Research* **6**(1), 32. https://doi.org/10.1186/1757-2215-6-32.
89. **Tang M, Huang C, Wang YF, Ren PG, Chen L, Xiao TX, Wang BB, Pan YF, Tsang BK, Zabel BA, Ma BH, Zhao HY and Zhang JV** (2016) CMKLR1 deficiency maintains ovarian steroid production in mice treated chronically with dihydrotestosterone. *Scientific Reports* **6**(1), 21328. https://doi.org/10.1038/srep21328.
90. **Wu XQ, Wang YQ, Xu SM, Liu JF, Bi XY, Wang ZQ and Zhang JP** (2017) The WNT/β-catenin signaling pathway may be involved in granulosa cell apoptosis from patients with PCOS in North China. *Journal of gynecology obstetrics and human reproduction* **46**(1), 93–99. 10.1016/j.jgyn.2015.08.013.
91. **Cao P, Li H, Wang P, Zhang X, Guo Y, Zhao K, Guo J, Li X and Nashun B** (2024) DNA hypomethylation-mediated transcription dysregulation participates in pathogenesis of polycystic ovary syndrome. *The American Journal of Pathology* **194**(6), 894–911. https://doi.org/10.1016/j.ajpath.2024.02.003.
92. **Bakar S, Arpa M, Kuruca N and Şentürk Ş** (2026) Gremlin-1 is associated with obesity but not polycystic ovary syndrome: Insights from a body mass index-matched analysis of bone morphogenetic protein pathway components, a cross-sectional study. *International Journal of Gynaecology and Obstetrics* **173**(3), 1383–1390. https://doi.org/10.1002/ijgo.70725.
93. **Mazdapour M, Ashkezari MD and Seifati SM** (2018) Analysis of BMP4 (rs121912765) polymorphism in Iranian women with history of recurrent spontaneous abortion: A case-control study. *Biomedical Reports*, 29–32. https://doi.org/10.3892/br.2018.1170.
94. **Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, Costello MF, Boivin J, Redman LM, Boyle JA, Norman RJ, Mousa A, Joham AE, the International PCOS Network, Arlt W, Azziz R, Balen A, Bedson L, Berry L, Boivin J, Boyle J, Brennan L, Brown W, Burgert T, Busby M, Ee C, Garad RM, Gibson-Helm M, Harrison C, Hart R, Hopkins K, Hirschberg AL, Ho T, Hoeger K, Jordan C, Legro RS, Li R, Lujan M, Ma R, Mansfield D, Marsh K, Mocanu E, Mol B, Mormon R, Norman R, Oberfield S, Patel M, Pattuwage L, Peña A, Redman L, Rombauts L, Romualdi D, Shah D, Spritzer PM, Stener-Victorin E, Tehrani FR, Thangaratinam S, Thondan M, Vanky E, Wijeyaratne C, Witchel S, Yang D, Yildiz B, Alesi S, Alur-Gupta S, Avery J, Khomami MB, Benham J, Bidstrup H, Chua SJ, Cooney L, Coster T, Ee C, Fitz V, Flanagan M, Forslund M, Jiskoot G, Kazemi M, Kempegowda P, Louwers Y, Lujan M, Melin J, Melson E, Mengistu YB, Naderpoor N, Neven A, Pastoor H, Rocha T, Sabag A, Subramanian A and Tan K** (2023) Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *European Journal of Endocrinology* **189**(2), G43–G64. https://doi.org/10.1093/ejendo/lvad096.
95. **Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group** (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and Sterility* **81**(1), 19–25. https://doi.org/10.1016/j.fertnstert.2003.10.004.
96. **Zeng X, Xie YJ, Liu YT, Long SL and Mo ZC** (2020) Polycystic ovarian syndrome: Correlation between hyperandrogenism, insulin resistance and obesity. *Clinica Chimica Acta* **502**, 214–221. https://doi.org/10.1016/j.cca.2019.11.003.
97. **Dimitriadis E, Menkhorst E, Saito S, Kutteh WH and Brosens JJ** (2020) Recurrent pregnancy loss. *Nature Reviews. Disease Primers* **6**(1), 98. https://doi.org/10.1038/s41572-020-00228-z.
98. **ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Mcheik S, Peramo B, Quenby S, Nielsen HS, van der Hoorn M-L, Vermeulen N and Goddijn M** (2022) ESHRE guideline: Recurrent pregnancy loss: An update in 2022. *Human Reproduction Open* **2023**(1), hoad002. https://doi.org/10.1093/hropen/hoad002.
99. **Hadas R, Rubinstein H, Mittnenzweig M, Mayshar Y, Ben-Yair R, Cheng S, Aguilera-Castrejon A, Reines N, Orenbuch AH, Lifshitz A, Chen DY, Elowitz MB, Zernicka-Goetz M, Hanna JH, Tanay A and Stelzer Y** (2024) Temporal BMP4 effects on mouse embryonic and extraembryonic development. *Nature* **634**(8034), 652–661. https://doi.org/10.1038/s41586-024-07937-5.

https://doi.org/10.1017/erm.2026.10068 Published online by Cambridge University Press