

## INVITED REVIEW

# Periovarian Adipose Tissue – an Impact on Ovarian Functions

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## Summary

Periovarian adipose tissue (POAT) is a type of gonadal white adipose tissue that surrounds the ovary. POAT is a source of various bioactive molecules, such as adipokines, cytokines, chemokines, growth factors and hormones. Thereby it could influence crucial ovarian functions. Recent findings showed that removal of POAT affects folliculogenesis and steroidogenesis in the ovary. Furthermore, changes in the morphology and function of POAT were observed in women during menopause or polycystic ovary syndrome. Although the relationship between the body's energy status and fertility in females is generally well known, the contribution of POAT remains still elusive. Therefore, the objective of this review is summarizing the actual state of knowledge about POAT function in physiological and pathological processes within the ovary.

## Key words

Periovarian adipose tissue • Ovary • Folliculogenesis • Steroidogenesis

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## Introduction

Adipose tissue is a type of connective tissue that is mainly responsible for energy storage, thus being involved in thermoregulatory and metabolic processes. Recent studies indicate that adipose tissue is also an important endocrine organ and secretes many various

bioactive molecules, namely adipokines, cytokines, chemokines, growth factors and hormones [1,2]. The factors produced by adipose tissue mainly regulate glucose and lipid metabolism in skeletal muscle, liver, brain, pancreas and the vascular system [3]. They have also been shown to exert effects on the immune system [4]. Recently a growing interest in the impact of the factors produced by adipose tissue on female reproductive functions has been seen, pointing to a close link between the body's energy status and fertility [5]. Although the effects of adipose tissue and secreted adipokines on the female reproductive system have been studied extensively, little is still known about the direct impact of periovarian white adipose tissue (POAT) on the processes taking place within the ovary. The aim of this paper is to present an overview of the latest scientific reports on the role of POAT in ovarian functions.

## Structure, types and function of adipose tissue

Adipose tissue is not a homogenous organ. It is composed of two cell fractions – adipocytes and the stromal vascular fraction (SVF) containing macrophages, fibroblasts, lymphocytes, granulocytes, endothelial cells, preadipocytes and adipose-derived stem cells (Fig. 1). Adipocytes are responsible for energy storage and have endocrine functions, whereas SVF is mainly composed of adipocyte precursor cells and immune cells [6].

Adipose tissue can be divided into two morphologically distinct types: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is found subcutaneously (subcutaneous adipose tissue, SAT) and around organs (visceral adipose tissue, VAT) [2].

An intermediate form between WAT and BAT is beige adipose tissue. Beige adipocytes are generated by the browning of WAT promoted by stressors such as cold exposure, exercise and surgery as well as pharmacological and dietary components. They may also arise *de novo* from specific progenitor cells following stimulation by cold exposure [2]. White, brown and beige adipocytes differ in morphological characteristics (Fig. 2). White adipocytes are large, with the nucleus located at the periphery, whereas brown adipocytes have a centrally located nucleus. White adipocytes contain a single large lipid droplet, whereas brown adipocytes contain numerous lipid droplets of different sizes. Furthermore, brown and white adipocytes differ in the size and number of mitochondria. Brown adipocytes have more abundant and bigger mitochondria with well-developed, densely packed cristae. The color difference between WAT and BAT is due to mitochondrial cytochrome content, which is higher in BAT [7]. Beige adipocytes are an intermediate form between white and brown adipocytes. BAT is much more innervated, with adrenergic terminals around blood vessels and on cells. In contrast, white adipocytes are not directly innervated [8].

The primary role of adipose tissue is to store energy that exceeds immediate needs in the form of triacylglycerols, *i.e.* fatty acid esters of glycerol. In the case of energy demand, triacylglycerols are hydrolyzed in the process of lipolysis (by lipolytic enzymes) to free fatty acids and glycerol, which provide a source of energy for peripheral tissues [1]. While the primary function of WAT is to store energy, BAT is mainly responsible for heat generation [7]. WAT makes up approximately 80 % of all adipose tissue in the body. It constitutes the body's main store of energy as lipids. SAT provides insulation against heat loss and serves as a barrier against skin infections, whereas VAT protects organs against damage [2]. VAT is constantly releasing free fatty acids into circulation and is highly metabolically active. It has been shown that epicardial adipose tissue is twice as metabolically active as VAT in other depots. It produces adipokines (resistin and adiponectin), cytokines and chemokines (IL1 $\beta$ , IL-6, TNF- $\alpha$ , MCP-1), as well as vascular endothelial growth factor (VEGF) [9]. The adipose tissue surrounding blood vessels plays a direct role in regulating their tension by producing adipokines (leptin, adiponectin, visfatin, resistin, omentin and apelin), cytokines and chemokines (IL-6, TNF $\alpha$ ), as well as vasoactive substances (nitric oxide, prostacyclin, angiotensin II), and can thus play a role in maintaining

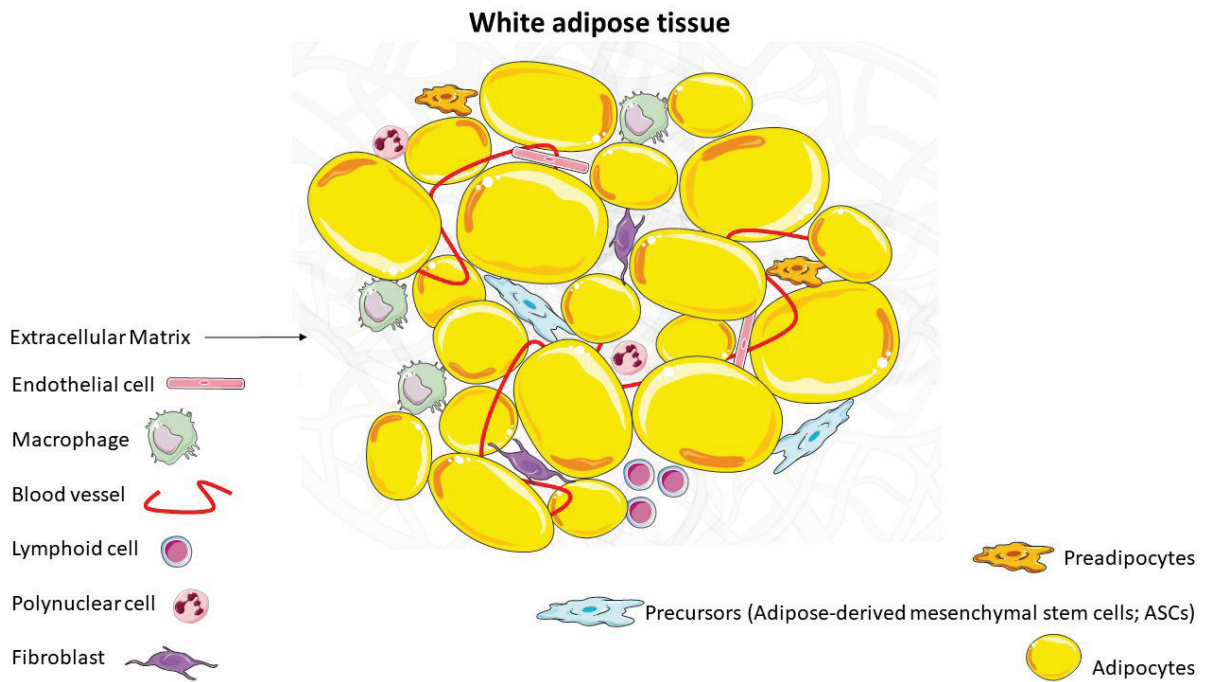
vascular homeostasis [10,11]. Therefore, as adipocytes synthesize and secrete factors which exert para- and endocrine effects, adipose tissue is involved in whole-body energy homeostasis.

## Gonadal adipose tissue

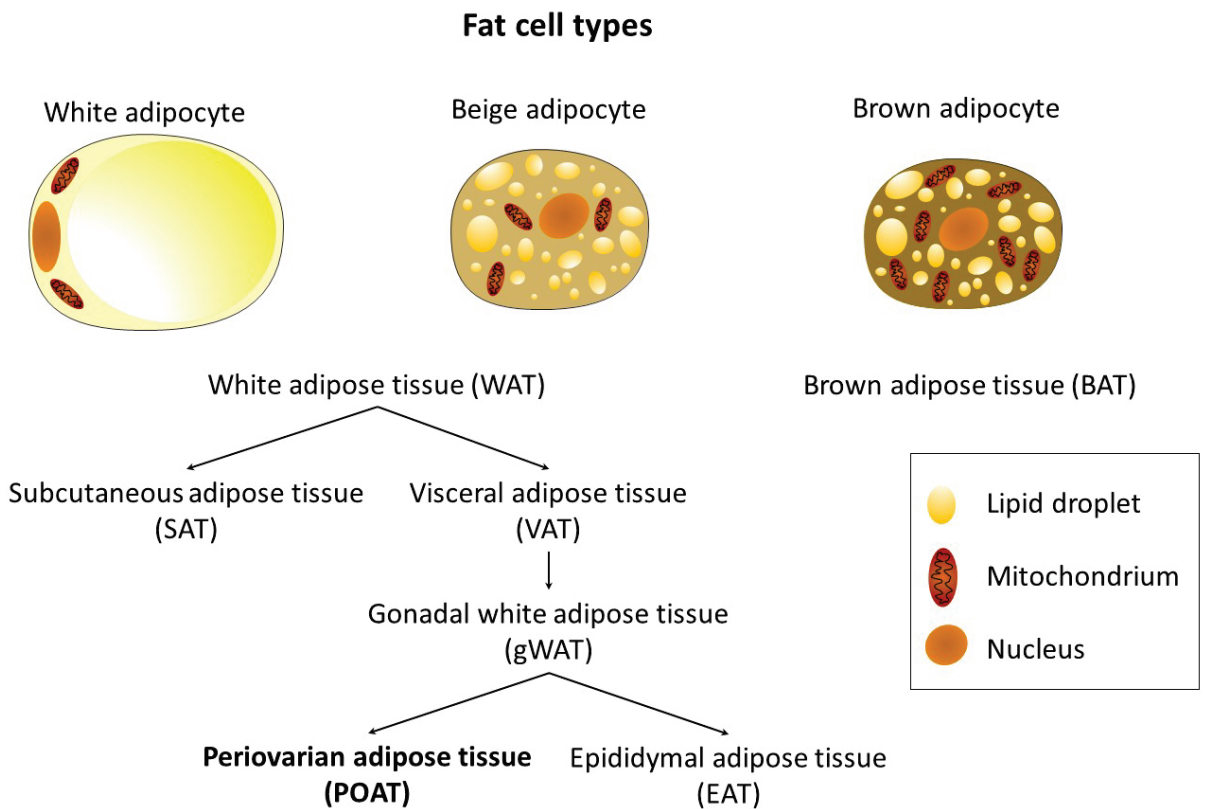
Recent studies have shown that there is a close link between abnormal adipose tissue function, especially in obesity, and reproductive functions. Therefore, adipose tissue surrounding the gonads (gonadal white adipose tissue, gWAT) is being increasingly investigated. One can distinguish between POAT and epididymal adipose tissue (EAT) [12] (Fig. 2). Particular attention has been given to the effect of gWAT on the local gonadal microenvironment required for normal gametogenesis [13].

Based on rat study, POAT is divided into lobules by connective septa carrying blood vessels and nerves, and each one is supplied by blood vessels and nerves. Lobules are predominantly consist of unilocular adipocytes, whereas few multilocular adipocytes can be scattered irregularly or clustered to small groups. In addition, each adipocyte type is surrounded by rich capillary plexus [14]. Interestingly, it has been reported that cells possessing the same morphological features of multilocular adipocytes and expressing the uncoupling protein (UCP, specific mitochondrial marker of BAT) occur among unilocular adipocytes within POAT of rats [15]. POAT is characterized by the expression of genes involved in glucose and lipid metabolism, such as *GLUT4*, *FAS*, *LPL* and *aP2*, as well as some molecules characteristic for BAT. Among them, the expression of *A2COL6* is high in POAT, suggesting a greater preadipocyte content and potential to proliferation. [16]. POAT contains BAT cells reacting to cold that was confirmed by increased UCP expression and the amount of differentiated BAT cells stimulated by noradrenaline in cold-acclimated rats [16]. Additionally, POAT is provided with sensory neuropeptide-containing nerves that contribute to the recruitment and differentiation of brown adipocytes [17]. In cold-acclimated rats, the increased vascular expression of the sensory neuropeptides was seen in periovarian brown cells that may be related to the need for dispersing the heat produced by the activated brown cells *via* vasodilation [17].

Previous research has reported that impaired POAT function in pathological conditions, such as obesity, might have a significant impact on ovarian functions. In a study by Nteeba *et al.* [18],



**Fig. 1.** Cellular composition of white adipose tissue (based on Bourgeois *et al.* [6]).



**Fig. 2.** Types of adipose tissue and morphological differences between adipocytes.

the adipocyte size within POAT from obese mice was found to be twice that of adipose tissue from lean mice. Furthermore, the study showed increased level of inflammatory cytokines and increased infiltration of

immune cells (macrophages and T cells) in POAT from obese mice. Consistently with this finding, ovarian mRNA levels of *Il1β*, *Il6*, *Ccl2*, *Ikkkb*, *Tnfa* *p55* and *p75* were found to be higher in tissue obtained from obese

animals. Another study showed the presence of crown-like structures (CLS) in obese mice, which are a marker of the proinflammatory process in adipose tissue, composed of macrophages surrounding dead or dying adipocytes [19]. However too little is still known about the role of POAT and female fertility.

### POAT – effect on ovarian functions

The ovary plays two major roles – it produces female reproductive cells and secretes steroid hormones. Studies to date have shown the possible impact of POAT on folliculogenesis, sex hormone and gonadotropin levels, and fertility in females [13].

#### *Folliculogenesis and oocyte quality*

To date, the majority of studies on the role of POAT have investigated the effects of its removal in rodents. In mice, the removal of POAT resulted in reduced ovarian mass [12,13] and impaired folliculogenesis [12,20,21]. Moreover, it has been demonstrated that POAT-deficient mice show fewer early antral and antral follicles and fewer ovulated eggs [20,21], and have no corpora lutea in ovaries [12]. It has also been observed that in POAT-deficient mice, many follicles are arrested at the secondary follicle stage and that the proportion of secondary follicles is higher compared to control animals [12,20]. Furthermore, the removal of POAT has also led to an increase in the number of atretic follicles [12,21] and abnormal follicular development [21] in mice. Additionally, the removal of POAT resulted in an increase in the expression of genes beneficial for folliculogenesis, which are associated with angiogenesis (*Adpn*, *Vegf*) and lipogenesis (*Acc*, *Fasn* and *Gapgh*). This may suggest the presence of mechanisms for the recovery of homeostasis in the ovary after the removal of POAT [12]. In a study by Yang *et al.* [12], the removal of POAT did not have a significant effect on the quality of ovulated oocytes. Approximately 72 % of fertilized oocytes developed to two-cell embryos both in POAT-deficient and control mice. However, a study by Wang *et al.* [20] found a statistically significant difference in the number of offspring between POAT-deficient mice and control mice, with POAT-deficient mice producing significantly fewer offspring.

#### *Gonadotropins secretion*

Among consequences of the removal of POAT could be disturbed pituitary gonadotropins secretion and

action – follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In two studies on mice [20,21], the FSH level in the proestrus and estrus stages was lower in POAT-deficient mice. As regards LH level, a study by Wang *et al.* [20] showed higher LH concentration in POAT-deficient mice, whereas a study by Zhu *et al.* [21] found no difference between POAT-deficient mice and control ones. Zhu *et al.* [21] has also observed no difference in the expression of genes encoding gonadotropin receptors (*Fshr* and *Lhr*) between POAT-deficient mice and control mice. These results are in contrast to those obtained by Wang *et al.* [20], who showed that the removal of POAT in mice resulted in a decrease in *Fshr* mRNA and an increase in *Lhr* mRNA levels, and to the results from a study by Yang *et al.* [12], which demonstrated increased *Fshr* gene expression in the ovaries of POAT-deficient mice. Another research describes the intriguing possibility that POAT may be responsible for providing the initial amount of estradiol needed for the ovary to become responsive to FSH during the onset of puberty in immature rats [22]. POAT might have an impact on the release of gonadotropins from the pituitary, indicating a wider range of functions in the hypothalamic-pituitary-ovarian axis. Whereas the data presented in above studies are preliminary, the further examination is required due to the crucial role of gonadotropins in the course of folliculogenesis.

#### *Steroidogenesis and lipid metabolism*

It has been found that the removal of POAT in mice impairs ovarian steroidogenesis, resulting in disrupted steroid level both in the circulation and locally in the ovary. The removal of POAT in mice has also been shown to result in decreased level of estradiol [20,21] and progesterone [21] at certain stages of the estrous cycle. Unequivocal findings have been reported considering to the expression of genes encoding steroidogenic enzymes – removal of POAT resulted in a decrease in the expression of *Cyp11*, *Cyp17* and *Cyp19*, and a decrease in the expression of genes encoding estrogen receptors ( $\alpha$  and  $\beta$ ), *Amh*, *Amhr2* and *3 $\beta$ hsd* [12,21]. However, in a study by Yang *et al.* [12], the removal of POAT did not have an impact on the expression of the gene encoding StAR protein. Given that cholesterol plays an obligatory role in steroidogenesis, the level of lipids in the ovary and blood serum in POAT-deficient mice have been investigated. Ovarian level of cholesterol were found to be higher in POAT-deficient mice, whereas no difference was found in ovarian triglyceride levels between these

two groups of mice. It should be noted, however, that no difference in ovarian lipid content was found between the two groups of mice four weeks after POAT removal when the POAT re-appeared. Serum triglyceride levels were lower in POAT-deficient mice, whereas no difference was found in serum cholesterol levels between the two groups of mice. The removal of POAT resulted in changes in whole body lipid metabolism and up-regulated whole body lipolysis [21]. Noteworthy, increased serum total cholesterol, as well as hypertrophy and dysfunction of POAT, coexisting with decreased ovarian aromatization and reduced size of primary, secondary, and tertiary follicles was found in hypothyroid rabbits [23]. Thus, it can be concluded that POAT is crucial for normal ovarian steroidogenesis.

Studies on mice have also found that the removal of POAT leads to a decrease in endometrial thickness, which suggests that POAT has an impact not only on ovarian function, but also on other female reproductive organs. In a study by Zhu *et al.* [21], impaired hormonal balance in POAT-deficient mice was found to affect the development of endometrium, which proliferation is controlled by estradiol and progesterone. Further research would provide insight into the mechanisms underlying interactions between the ovary and adipose tissue and the impact of adipose tissue on fertility mediated by changes in the levels of steroid hormones.

### POAT and ageing of the ovary

The appearance and function of adipose tissue change with age. VAT plays an important role in estradiol production in menopausal women [24]. Adipose tissue is considered to contribute approximately 50 % of circulating testosterone in premenopausal women and 100 % of circulating estrogens in women after menopause [25]. During menopause, body fat increases by approximately 5 %. However, as menopause also results in a decrease in fat-free body mass, most studies have shown that menopause does not have a significant effect on body weight or body mass index [26]. Furthermore, the distribution of adipose tissue changes with age – in premenopausal women, it is mainly found subcutaneously and in the femoral region, whereas after menopause, it accumulates in the visceral region, which results in an increased risk of cardiovascular disease, metabolic disorders and diabetes [27]. The age-dependent redistribution of adipose tissue from subcutaneous to

visceral depots is closely linked to hormonal changes. It is mainly due to a decrease in estrogens level, which contributes to a decrease in metabolic rate, insulin resistance, increased body weight and adipose tissue inflammation [28]. A number of studies have confirmed that estrogens play an important role in sex-dependent metabolic disorders and the regulation of adipose tissue metabolism. Studies in mice focusing on age-related changes in POAT showed that its increases in mass and its morphology changes. In one study the authors found that in older mice, the area of adipocytes was three times larger and the number of adipocytes was lower compared to young animals. The authors also found differences in lipid profile between the two groups of mice, with significant differences observed in the levels of triacylglycerols – the total amount of triacylglycerols and free fatty acids in adipose tissue was found to decrease with age [29]. In the light of the findings presented above, it seems that the changes taking place in the ovary during the ageing process may be associated with changes in the structure and function of POAT. However, further research is needed in this area.

### Vitamin D<sub>3</sub> and POAT

POAT, similarly to other WAT depots, secretes many bioactive molecules, such as adipokines (e.g. adiponectin, leptin, resistin, phenixin), cytokines (e.g. TNF $\alpha$ , IL-1 $\alpha$ , MPC-1, IL-6, IL-10), growth factors and steroid hormones (e.g. estradiol) [1,2,18]. Recently we have found that rat POAT expresses vitamin D<sub>3</sub> synthesizing enzyme (Cyp27b1) and its homogenates contain 1,25(OH)<sub>2</sub>D<sub>3</sub>, indicating local production of vitamin D<sub>3</sub> in POAT [30]. Calcitriol (1,25(OH)<sub>2</sub>D<sub>3</sub>), the bioactive form of vitamin D<sub>3</sub>, is structurally similar to steroid hormones and shows hormone-like activity [31]. It acts predominantly through a nuclear receptor and has pleiotropic effects. A number of studies have demonstrated that it modulates female reproductive processes, including folliculogenesis, steroidogenesis and proliferation of ovarian cells [32,33]. Vitamin D<sub>3</sub> deficiency has been linked to a number of ovarian pathologies, including among others polycystic ovary syndrome (PCOS), premature ovarian failure, ovarian cancer endometriosis and uterine fibroids [34,35]. In one study, the induction of PCOS in female rats resulted in decreased calcitriol level in POAT as well as decreased Cyp27b1 mRNA expression and diminished abundance of Cyp27b1 protein, which is necessary for the

conversion of 25(OH)D<sub>3</sub> to bioactive 1,25(OH)<sub>2</sub>D<sub>3</sub> [30]. In a mouse model of menopause, vitamin D<sub>3</sub> deficiency after ovariectomy resulted in increased body weight, and increased mass and size of adipocytes within POAT compared with mice after ovariectomy fed a diet containing vitamin D<sub>3</sub>. Moreover, the study showed lower level of inflammatory markers in POAT from mice fed a standard diet [36]. Therefore, further research is needed to understand the metabolism and function of calcitriol in POAT as well as its impact on ovarian function.

## Conclusions

Studies on adipose tissue and its function are important as adipose tissue is the largest organ in the body. POAT exerts local effect on the ovary, providing a specific environment, energy and substrates for ovarian

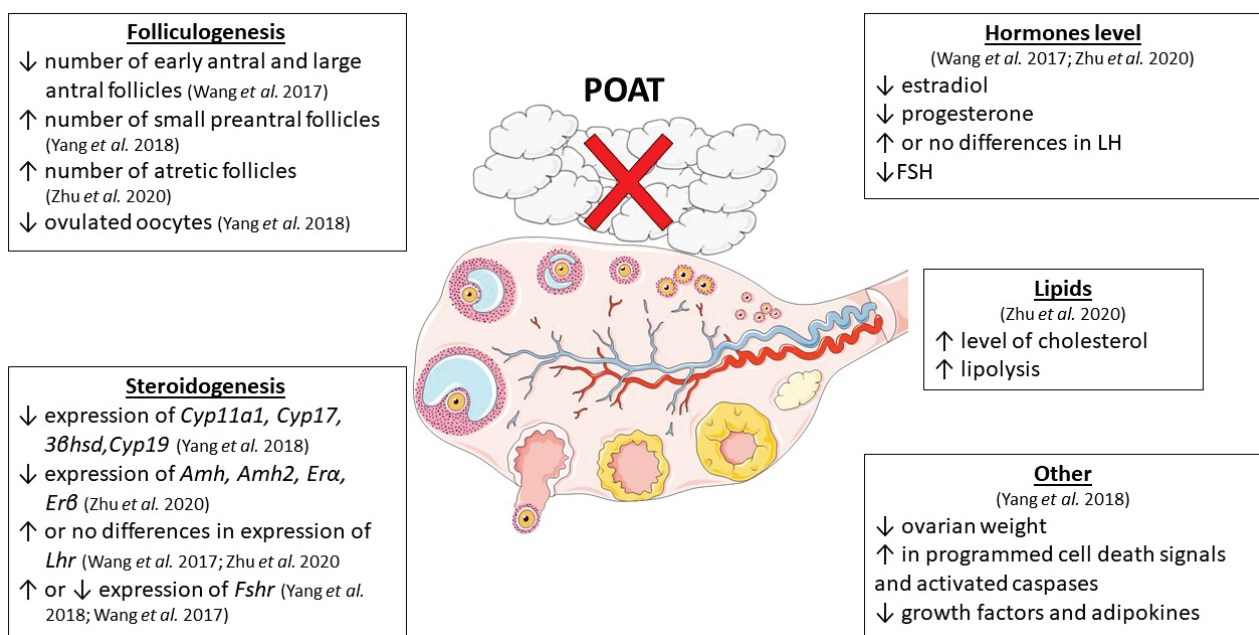
steroidogenesis and folliculogenesis. Removal of POAT impairs all these ovarian processes and results in structural endometrial abnormalities (Fig. 3). Current knowledge and the body of research to date are insufficient to understand the processes, mechanisms and relationships between POAT and the reproductive system. Therefore, further research is necessary to understand how POAT might implicate in metabolic disorders and fertility problems in females.

## Conflict of Interest

There is no conflict of interest.

## Acknowledgements

The Figures 1-3 were partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 Unported License.



**Fig. 3.** Effect of periovarian adipose tissue (POAT) removal on ovarian functions.

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