Tanzania Journal of Health Research
Volume 15, Number 2, April 2013
Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

Morpho-physiological features associated with menopause: recent knowledge and areas for future work

IPYANA H. MWAMPAGATWA[1*], MASUMBUKO Y. MWASHAMBWA[2] and AINORY P. GESASE[3]
[1]*Department of Maternal Health, School of Medicine, University of Dodoma, Dodoma, Tanzania*
[2]*Department of Surgery, School of Medicine, University of Dodoma, Dodoma, Tanzania*
[3]*Department of Biomedical Sciences, School of Medicine, University of Dodoma, Dodoma, Tanzania*

Abstract: Menopause is the permanent cessation of menstruation resulting from loss of ovarian follicular activity which happens as a result of depletion of primary follicles which is basically an aging effect. Depletion of ovarian follicles is reflected as declined production of oestradiol which is currently known to be central to the morphologic and physiological changes that happen during the climacteric, menopause and post menopause periods. The cessation of oestradiol production is much more pronounced in tissues with oestrogen receptors such as bones, brain, blood vessels, central nervous system and the skin. But generally little is known on the subject and in particular the bioactive substances involved in the process such that there are some symptoms that menopause women experience which not only defy clinicians but also challenge the management of the condition. This article is presented to shade light to what is currently known, what is not known and stimulate future research which may reveal more understanding and advance our knowledge on management of women throughout the climacteric and menopausal periods.

Keywords: menopause, menstruation, ovarian follicles, oestriadiol, inhibin, mast cells

Introduction

Menopause is defined as the point in time when menstrual cycles permanently cease due to the natural depletion of ovarian oocytes from aging. The diagnosis is typically made retrospectively after the woman has missed menses for 12 consecutive months. It marks the permanent end of fertility and the average age of menopause is 51 years (WHO, 1996; Butler & Santoro, 2011; Santoro & Randolph, 2011). Research into why menopause occurs is centred mainly on ovaries because of abnormal follicular development and depletion of ovarian follicles (Judd & Furnet, 1994). The current view is that the follicles fail to develop because the ovaries become insensitive to follicle stimulation (FSH) hormone. However, recent findings have suggested the role of inhibin B and possibly other local paracrine factors in the recruitment and regulation of follicular development (Findlay *et al*., 2001).

Although the major symptoms of menopause is cessation of menstrual flow, irregularities in hormonal serum levels during perimenopausal period is thought to bring silent morphological and physiological changes in the body before the time of onset menopause. Systems that are commonly affected include the bones, blood vessels, heart, brain, urinary tract, gastrointestinal tract, skin and reproductive system (Nicks *et al*., 2010). The morphological changes that occur are commonly associated with complaints that in some cases need medical attention ((Burger, 1999; Nicks *et al*., 2010). Knowledge into such changes in various tissues is important not only for the understanding of the biology of menopause but also may have treatment implications and may be useful in counselling the woman on the expected body changes. This article reviews the cell biology of menopause and the associated morphological features of reproductive organs after menopause. The information is aimed at stimulating research on menopause that will add knowledge on the pathophysiology of menopause.

* Correspondence: Ipyana H. Mwampagatwa; E-mail: mwampagatwai@yahoo.com

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

Ovaries and the biology of menopause: the role for inhibin in the journey to menopause

Ovaries are paired organs situated on either side of the uterus and their primary functions are to release an oocyte during ovulation and secondly they secrete the female sex hormones. On cross section each ovary consists of the superficial ovarian cortex, the inner medulla and the hilus (Leeson *et al.*, 1988). The ovarian cortex is made up of two components, namely the stroma and follicles. Presence of follicles makes the cortex to be larger than the medulla. The stroma of the cortex is basically the same as that of the medulla. It has amount of loose connective tissue consisting of nerve fibres, lymph vessels, blood vessels and numerous stromal cells also known as interstitial or fibroblast-like cells (Leeson *et al.*, 1988). Stromal cells secrete small amounts of androgens and may differentiate into a variety of other cell types such as follicular theca internal cells, luteinizing stromal cells, enzymatically active stromal cells, smooth muscle cell, decidual cell, endometrial stromal type cells, adipocytes and stromal Leydig cells (Moore, 1988). Embedded within the cortical stroma are ovarian follicles; at birth there are nearly 2 million follicles in the cortex, however, they gradually undergo atresia throughout the life of a woman and at puberty there are about 400,000 follicles in the cortex for reproductive life (Moore,1988).

Following puberty the ovaries begin to produce a single mature oocyte each month up to menopause. During each menstrual cycle 2-20 follicles are stimulated to grow, however, only one of these follicles attains full maturity and ovulate, the rest will degenerate by the process of atresia (Gosden & Faddy, 1994). The long held view is that development of ovarian follicle is controlled by the gonadotropins (Follicle Stimulating Hormone, FSH and Lutenizing Hormone, LH) secreted by the adenohypophysis. However, recent studies have suggested the presence of intrinsic ovarian paracrine system that trigger early development of follicles; and that the gonadotropins comes in late during the final maturation stages of follicles and ovulation (Buffet *et al.*, 1998; Findlay *et al.*, 2001). Studies that have utilized gene manipulation technique showed that early follicular development (from primordial to antral follicles) proceeded normally in animals that lack FSH and/or FSH receptors (Buffet *et al.*, 1998). Follicular development is characterized by the growth of an oocyte and proliferation of the surrounding cells to form glandular tissue that secrete oestrogen and progesterone. These hormones maintain the morphological integrity of many organs in the body and they also prepare reproductive system for copulation, fertilization, implantation and initial growth of the embryo (Moore, 1988).

Under normal circumstances the process of follicular development occurs cyclically every month during the reproductive life, but as menopause approaches it becomes irregular up to the time when it stops completely (Richardson, 1993; Judd & Fiurnet, 1994; Proir, 2002). Abnormal fluctuations of sex hormones lead to gradual morphologic and physiological changes to most organs in the body. Events that precede menopause and pathways that lead to failure in follicular development are not clearly understood. It has been suggested that as the woman age advances the follicles are depleted from the cortex due to repeated ovulation and atretic change, and that ovarian sensitivity to FSH also decreases (Richardson, 1993; Gosden & Faddy, 1994). Similarly, it is widely believed that gradual depletion of the ovarian follicles impairs hormonal secretion, which further accelerate menopause (Richardson, 1993). However, the number of follicles that must remain in the ovaries for the maintenance of normal development to full maturity is not known. Whether the development of one ovarian follicle is dependent on the presence of a specific number of established other follicle has not been discussed.

Attainment of menopause is a gradual process and the journey is characterized by menstrual irregularities, ovulatory and anovulatory cycles up to the time when menstrual flow stops completely (Prior, 2002). This indicates that molecular pathways that control the menstrual cycles are gradually depleted from the ovarian cells. Studies on the hormonal status in women have indicated that

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

menopause is associated with low serum levels of oestrogen, inhibin, insulin like growth factors-I (IGF-I), anti-Mullerian hormone (AMH) and elevated serum levels of FSH (Klein *et al*., 2000; Sowers *et al*., 2008). AMH has been suggested to be an endocrine marker of follicle depletion or ovarian aging (Overlie *et al.*, 2005; Sowers *et al*., 2008). Inhibin is a heterodimer containing α and β subunit (inhibin α and β) and it belong to the TGF-β superfamily of proteins (Overlie *et al.*, 2005). Inhibin β is secreted by the granulosa cells during early follicular development and in recent years it has attracted much attention because of its role in the regulation of early follicular development and secretion of FSH by the adenohypophysis (Messinis, 2000; Findlay *et al*., 2001; Jaatinen *et al.*, 2002). Studies done in girls from birth to adulthood indicated that serum levels of inhibin are low below the age of 6 and reaches a peak between 12-18 years when the girls attain menarche (Bergada *et al*., 2001; Crofton *et al.*, 2002). Observations made in the elderly women showed that inhibin serum levels were lower in the women aged 46-52 years than in women aged 39-45 years (Seifer *et al*., 1999). The study also revealed that these women were still menstruating and the serum levels of FSH were normal, there was no difference between the old and younger woman. Putting together the findings indicate that abnormalities in inhibin secretion (i.e. low serum levels) occur much earlier when serum FSH levels are still normal (Richardson, 1993; Burger, 1999; Seifer *et al*., 1999). An indication that low serum level of inhibin and possibly other intraovarian autocrine and paracrine factors may play a central role in the establishment of menopause. It is known that low inhibin levels remove the inhibitory effects to the pituitary gland, leading to elevated FSH serum levels (Ala-fossi *et al*., 1998, Buffer *et al*., 1998).

During reproductive life secretion of FSH is cyclical, with serum levels varying from low to high; this character maintains the sensitivity of follicular cells to FSH. Chronic elevation of FSH and prolonged exposure of ovarian cell to FSH may cause down regulation of the receptors, making the follicular cells insensitive to FSH leading to failure of the final maturation of ovarian follicles. This may explain anovulatory cycles that characterizes perimenopausal period (Vagenakis, 1989). Chronic exposure of receptors to ligands has been shown to have a negative effect on the receptors expression (Alberts *et al*., 1994). Why inhibin levels decrease in women approaching menopause is not clear, it is possible that there may be local factors secreted by granulosa cells or the oocyte that may regulate inhibin secretion. Factors that control the secretion inhibin during reproductive life are still debatable; a few researchers have concentrated on the possible role of FSH (Messinis, 2000; Welt & Schneyer, 2001). However the relationship that exists between FSH and inhibin during perimenopausal period and at menopause does not strongly support the role of FSH in the regulation of inhibin secretion. At menopause low serum levels of inhibin occurs when the FSH levels are normal and they remain so even after menopause when there high serum level of FSH, an indication that factors other than FSH are responsible for the regulation of inhibin secretion.

Past studies have indicated the presence of local factors such as Insulin-like growth factor-I (IGF) in the control of inhibin secretion (Klein *et al*., 2000; Welt & Schneyer, 2001). During reproductive life IGF-I is expressed in the endomentrial cells and in the ovarian tissue and studies have showed that in the ovaries it enhances proliferation of granulosa cells and secretion of steroid hormones (Messinis, 2000; Conover *et al*., 2001). Other observations have showed that as women approach menopause the levels of IGF-I decreases from ovarian tissues, and this is followed by a gradual decline in serum levels of inhibin B (Klein *et al.*, 2000; Welt & Schneyer, 2001). Low IGF-levels have also been reported in the endometrium of postmenopausal women (Leone *et al.*, 1993; Liverro *et al.*, 1999). It is therefore suggested that IGF-I may act as a paracrine factor that enhances the secretion of inhibin B during reproductive period and that declining levels of IGF-I in ovarian tissues may lead to failure of inhibin B secretion by granulosa cells. It is known that the oocyte plays an important role in controlling its own fate by influencing follicular cell function.

Studies done in mice have showed that mice lacking oocyte secreted differentiation growth factor-9 (GDF-9) become infertile due to failure of follicular cells development and oocyte maturation

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

(Hayashi *et al.*, 1999; Matzuk, 2000). GDF-9 is a protein that in human is encoded by the GDF9 gene (McGrath *et al*., 1995), it plays an important role in the development of primary follicles in the ovary. It has critical role in granulose cell and theca cell growth, as well as in differentiation and maturation of oocytes (Su *et al*., 2004). GDF-9 has been associated in premature cessation of ovary function, therefore has a significant role in fertility (McNatty *et al*., 2007)

The uterus and menopause: the role of mast cells

The uterus is the largest reproductive organ that is capable of undergoing the hormonal induced growth in order to accommodate the developing foetus. Its wall is made up of three layers; the outer perimetrium, the middle muscular layer (myometrium) and the inner mucosal layer (endometrium). Oestrogen and progesterone are known to influence development and growth of the uterus during menstrual cycle and during pregnancy; in the absence of sex hormones it becomes atrophic. The endometrium is a complex mucus membrane that undergoes cyclical changes in preparation for implantation and in the absence of pregnancy the functional part is shed off as menstrual flow. Ultrastrucurally the endometrium is made up of the surface epithelium and a wide endometrial stroma that is continuous with the underlying layer of smooth muscles. Surface cells are columnar in shape and form a single layer of cells; some are ciliated while others are non-ciliated (Baraggino *et al.*, 1980). Ciliated cells are numerous and beating of the cilium facilitates mobilization and distribution of endometrial fluid in the uterine cavity. None-ciliated cells secrete mucus and their luminal surface is densely covered with long microvilli, this increases the surface area of the endometrium. The luminal surface may show apical protrusions suggesting the occurrence of apocrine secretion.

Secretory cells also extend deep into the stroma where they line the endometrial glands (Leeson *et al*., 1988). The endometrial stoma contains the endometrial glands, extensive capillary network and fibroblast-like cells that are embedded in connective tissue network of collage fibres. It is the most dynamic portion of the endometrium; it can grow up to 7mm thick during menstrual cycle. For the purpose of description it is divided into the basal and the superficial functional zone. The stroma of the basal zone is cellular and fibrous than the functional zone and it does not undergo cyclic changes during menstrual cycles. It serves principally as a source of tissue for the cyclic regeneration of the functional layer. The functional zone is superficial to the basal zone and it is subjected to cyclic changes that are brought about by the oestrogen and progesterone secreted by ovarian follicles (Amos *et al.*, 1994). Endometrial tissue shows cyclical expression of oestrogen and progesterone receptors during menstrual cycle, this enables the sex hormones to induce growth of the endometrium and secretory activities (Amos *et al.*, 1994).

Menopause brings atrophic changes to the endometrium; these are gradual and become more marked as time after menopause advances (Delgdisch *et al*., 1978). The surface cells become cuboidal in shape and they gradually lose cilia from the apical membrane (Delgdisch *et al*., 1978). Non-ciliated cells become flattened, microvilli become short and blunt, and as the length of post-menopausal period increases they disappear from the cells. Menopausal endometrium does not show features of active proliferation or secretion. The cytoplasm of glandular and stromal cells becomes clear with a few organelles and immunoreactivity for oestrogen and progesterone receptors decreases. There is fibrosis of the endometrial stroma, which is caused by increased amount of collagen fibres (Delgdisch *et al*., 1978). This makes the menopausal endometrium less cellular and as a result the stromal volume decreases steadily to approximately less than 0.3mm (Zalud *et al*., 1993). There is a decrease in number of endometrial glands, which become oriented parallel rather than perpendicular to the surface cells. It has also been shown that menopause is associated with a decrease in vascular distribution and resistances to endometrial blood flow (Zalud

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

et al,. 1993; Bonilla-Musoles *et al*., 1995). Although oestrogen and progesterone are the main hormones that causes endometrial cyclical change during reproductive life, the endometrium has been shown to releases some active molecules such as decidual associated protein-200, insulin growth factor (IGF), transforming growth factor (TGF), Interleukin-8 (IL-8) and telomerase enzyme, which have been shown to enhance endometrial growth and maintenance (Leone *et al.*, 1993; Liverro *et al*., 1999; Arici, 2002). However, how these growth factors are linked to sex hormones has not been clearly described. The interesting phenomenon about the endometrium is that whereas the ovaries cease to operate permanently after menopause, the endometrium retains the capacity to undergo proliferation and growth upon stimulation (Sauer *et al*., 1993; Liverro *et al*., 1999). This is a unique feature that is present in human species. In other mammals it is the uterus that fails to support nidation; production of oocytes continues well into old age (Finn, 2001). Postmenopausal endometrium has been shown to support implantation and growth of pregnancy to term (Sauer, 1993; Finn, 2001).

Receptors for some powerful growth factors have been labelled in the endometrium cell and some of them remain so even after menopause. Studies done in the endometrium of postmenopausal women revealed the expression of TGF-beta 1, telomerase activity and insulin growth factor-1 receptors in the endometrium cells (Leone *et al*., 1993). It is not clear as to why such molecules continue to be expressed in the endometrium after menopause (Kyo *et al.*, 1997; Liverro *et al*., 1999). They may play a role of maintaining the quiescent differentiated state of atrophic post-menopausal endometrium (Liverro *et al*., 1999).

The myometrium contains mainly the smooth muscle fibres and it forms the bulk of the uterus, measuring about 1.5cm at the thickest point. The bundles of muscle fibres are separated by connective tissue and individual smooth muscle cells are long measuring about 60µm. However, during pregnancy they increase greatly in size and may attain a length of approximately 600µm. The muscle fibres are arranged into two layers; the stratum subvasculare, which lies below the endometrium and stratum supravasculare (Leeson *et al*., 1988; Noe *et al*., 1999). It is generally known that thinning of the myometrium occurs after menopause. However, the exact ultrastructural changes that occur in the smooth muscle and to the elements of the interstitial space and the pathway that lead to such changes are not well understood. Both the strata vasculare and supravasculare have oestrogen and progesterone receptors. Nonetheless, during reproductive life the stratum vasculare is much more dynamic than stratum supravasculare (Noe *et al*., 1999). The smooth muscle cell exhibits a cyclic pattern of sex hormones receptor expression that is comparable to those in the endometrium (Koshiyama *et al*., 1996; Noe *et al*., 1999).

Oestrogen is known to support and maintain the uterine smooth muscle cells and also to increase the amount of contractile proteins, irritability and spontaneous muscular activities. Most researchers have associated the low serum levels of sex hormones during menopause with atrophic changes in the myometrium (Zalud *et al*., 1993; Koshiyama *et al*., 1996). Judging from the morphological features of the myometrium it is unlikely that the declining serum levels of sex hormones alone can explain atrophic changes seen after menopause. Other factors may be present in the aging myometrium that may work in conjunction with sex hormones to bring about menopausal changes.

Generally white blood cells are seen in the walls of reproductive organs, and they include lymphocytes, neutrophils, macrophages and mast cells (Choroszewska *et al*., 1989; Crow *et al*., 1991; White *et al*., 1997; Utrearas *et al*., 2000). Mast cells are in particular abundantly distributed in the myometrium and they lie in close association with smooth muscle cells (Crow *et al*., 1991; Milne *et al*., 2001). Stem cell factor (SCF) and its receptors, which regulate mast cell proliferation and differentiation, have also been localized in the myometrium (Mori *et al.*, 1997). Mast cells, like most other leukocytes are known to release growth factors that may enhance tissue proliferation and

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

maintenance (Skeper *et al*., 2001; Artuc *et al*., 2002). These include the nerve growth factor (NGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), vascular growth factor (VGF) and serotonin (Azmitia, 2001; Ribatti *et al.*, 2001; Skaper *et al.*, 2001; Artuc *et al.*, 2002). FGF is known to regulate the proliferation and function of many classes of cell and in particular it enhances proliferation and maintenance of smooth muscle cells (Alberts *et al.*, 1994). EGF is a powerful regulator of growth, differentiation and matrix synthesis by connective tissue cells and it has also been shown to stimulate mitosis in many classes of cells. NGF is known to influence growth of neuritis in tissues; in this way it helps to sustain cell survival (Alberts *et al*., 1994). VGF has been shown to stimulate angiogenesis, an important process during tissue growth and repair (Alberts *et al*., 1994). All these morphological phenomena are relevant to the uterus during the reproductive period.

Observations made in the postmenopausal uterus indicated that mast cell population decreased significantly in the myometrium, and that the remaining few cells did not show secretory activities (Crow *et al*., 1991). It is possible that mast cells may play an important role in the maintenance and support of the myometrium during reproductive life (Mori *et al*., 1997). Decreasing mast cell population and absence of their secretory activities during menopause may deprive the uterus with important active molecules needed for growth and maintenance. However, to what extent the decreased mast cell population affect the postmenopausal changes in the uterus awaits future studies. Similarly, there is no data on the expression profiles of some these trophic factor after menopause. Answers to these questions may provide valuable information towards the understanding the menopausal changes in the myometrium.

Fallopian tubes and the cervix after menopause

The cervix and fallopian tubes allows the uterine cavity to communicate with the vagina and ovaries, respectively. The mucosa of the fallopian tube shows extensive folding that increase towards the ovarian side and is lined by ciliated and non-ciliated secretory cells (Donnez *et al*., 1985). Other cells that have been demonstrated include the antigen presenting Langerhans cell and the myofibroblasts (Hagiwara *et al*., 1998). Ciliated cells are columnar in shape and accounts for roughly 20-30% of mucosal cell; the cilia beat in synchronized waves in the direction of the uterus (Donnez *et al*., 1985). Secretory cells account for 55-65% of mucosal cells and their luminal surface contains numerous microvilli. Both ciliated and non-ciliated cells express oestrogen and progesterone receptors and the concentration of these receptors varies with the phase of menstrual cycle (Nielsen *et al*., 2001). Studies done in monkey indicated that the presence of cilia on the mucosal cells depends on the presence of oestrogen and that castration caused atrophy and gradual loss of cilia (Nielsen *et al*., 2001). The main function of mucosal cells is to provide favourable environment for the transport of gametes and zygote and to nourish the embryo, by releasing embryotrophic factors before it reaches the uterine cavity (Valasquez *et al.*, 2001).

The molecular pathways that regulate postmenopausal changes in the fallopian tubes are not clearly understood because there is limited research information. A few studies have reported the presence of trophic factors such as Interleukin-8 (IL-8), epidermal growth factor (EGF) and transforming growth factor (TGF) in the fallopian tube (Palter *et al.*, 2001). Experiment done in human fallopian tube indicated that IL-8 receptor showed regional variation, they were more expressed in the distal portion of the fallopian tube (Palter *et al*., 2001). IL-8 is mainly produced by the fibroblasts, epithelium, hepatocyte and macrophages; in human fallopian tubes, the receptors were predominantly seen in the epithelium (Palter, 2001). IL-8 belongs to the class of interleukin that are known to mediate local interaction between the white blood cells. It is a potent angiogenic factor and is also known to stimulate cell proliferation and survival directly and/or by inducing

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

secretion of potent growth factors such as fibroblast growth factor-2 (FGF-2) and Insulin growth factor-1 (IGF-1) (Arici, 2002). Presence of IL-8 receptors in the fallopian tube suggests a physiological role. However, how it interacts with sex hormones and its role in menopause is open for future work. Another phenomenon that needs to be clarified is whether postmenopausal fallopian tube can support the establishment of pregnancy upon stimulation. Such knowledge is important not only for the general understanding on the biology of menopause, but also it will shed light on fertility problem caused by failure of the fallopian tubes.

The exposed part of the cervix (ectocervix) is lined by a protective stratified squamous epithelium, which show three zones: the basal (germinal) cell zone that provide new cell to the overlying layers, the midzone and the largest outer superficial zone that contain cells that are constantly shed off in a process called desquamation. The half-life for these cells is between 4-5 days, and oestrogen has been shown to accelerate proliferation, maturation and desquamation of superficial cells. Studies have showed that after menopause the squamous cells become atrophic and maturation does not occur (Pandit & Ouslander, 1997). Thinning of the epithelial lining result into inadequate protection of the sub-epithelial tissue against trauma, this may cause frequent bleeding and inflammation commonly seen after menopause (Pandit & Ouslander, 1997). The mucosa of the endocervix is highly folded, forming complex deep furrows known as plicae palmatae. It is lined by a single layer of columnar cells consisting of mucus and a few non-mucus secreting cells. Studies have showed that secretory cells are influenced by sex hormones; and that cervical mucus is subject to profound cyclic changes (Pandit & Ouslander, 1997). Oestrogen induces profuse, watery and alkaline secretion via exocytosis and apocrine secretory mechanisms, which facilitate sperm transport across the cervix.

After menopause the mucosa wall of the cervix shrinks and the folded nature gradually disappear to become smooth. The columnar cells become flat, the cilia disappear and secretory features decrease causing dryness of the vagina, which may cause dyspareunia (Pandit & Ouslander, 1997). Other cells that have been demonstrated in the cervical wall include the macrophages, dendritic cells, lymphocytes and neuroendocrine cells (Fetissof *et al*., 1985). The neuroendocrine cells have been shown to express serotonin immunoreactivity, but their roles and the immunohistochemical profile after menopause are not understood (Fetissof *et al*., 1985).

Observations made in tissues other than the genital organs have showed that serotonin may regulate the secretion of mucus, contraction of smooth muscles, cell proliferation and cell migration and maturation (Fujita *et al.*, 1988). Studies done in the urethra indicated that the neuroendocrine cell extend to reach the luminal surface and have synaptic contact with afferent nerves (Dixon *et al*., 1973). Because of this morphological relationship it has been suggested that the neuroendocrine cells may represent sensory devices for detecting information about the luminal contents, and via afferent nerves associated with them, lead to local reflexes, such as muscular contraction (Dixon *et al.*, 1973; Fujita et al., 1988). Solitary cells with endocrine functions are widely distributed in the body and have been shown to release a number of substances such as gamma amino-butyric acid, serotonin, gastrin, secretin and cholecytokinin (Davanger *et al.*, 1994). In the gut some of these molecules have been shown to play important role during development and also to enhance growth and maintenance of gastric mucosa and age related decline in endocrine cell population have also been documented (Fiorica *et al*., 2000 & Larsson, 2000). To what extent the neuroendocrine cells are involved in the physiology of the cervix during the reproductive life and after menopause remains to be an interesting subject for future research.

Conclusion

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

Though our current knowledge on the morphological and physiological changes of menopause has centred on the ovary and cessation of production of oestradiol by the ovarian follicles, there is mounting scientific evidence that there are other bio-active substances that may be responsible for the process and explain the changes and clinical presentation observed throughout the climacteric and post menopausal periods. Further studies on the subject in future may reveal what is currently not known and therefore have an impact on management of postmenopausal symptoms.

References

Ala-Fossi, S.L., Maenpaa, J., Blauer, M., Aine, R., Touhimaa, P. & Punnonen, R. (1998) Inhibin A and B in peri-and postmenopause. *Maturita*s 16, 273-281.

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K. & Watson, J.D. (1994) *Molecular Biology of the Cell* 771, 1120-1180.

Amos, N.N., Crow, J. & Shaw, R.W. (1994) Comparative immunohistochemical study of oestrogen and progesterone receptors in the fallopian tube and uterus at different stages of the menstrual cycle and at the menopause. *Human Reproduction* 9, 1027-1037.

Arici, A. (2002) Local cytokines in endometrial tissue: The role of interleukin-8 in the pathogenesis of endometriosis. *Annals of New York Academy of Science* 955, 101-109.

Artuc, M., Steckelings, U.M. & Henz B.M. (2002) Mast cell-fibroblast interaction: Human mast cells are source and inducers of fibroblast and epidermal growth factore. *Journal of Investigative Dermatology* 118, 391-393.

Baraggino, E., Dalla Pria, S., Cauberli, C. & Baortolotti, S. (1980) Scanning electron microscopy of the human normal endometrium. *Clinical Experimental Obstetrics & Gynecology* 7, 66-70.

Bergada, I., Bergada, C. & Campo, S. (2001) Role of inhbins in childhood and puberty. *Journal of Paediatric Endocrinology & Metabolism* 14, 343-353.

Bonilla-Musoles, F., Marti, M.C., Ballester, M.J., Raga, F. & Osborne, N.G. (1995) Normal uterinearterial blood flow in postmenpausal women assessed by transvaginal color Doppler sonography: the effect of hormone replacement therapy. *Journal of Ultrasound Medicine* 14, 497-501.

Buffet, N.C., Djakoure, C., Maitre, S.C. & Bouchard, P. (1998) Regulation of the human menstrual cycle. *Frontiers in Neuroendocrinology* 19,151-186.

Burger, H.G., (1999) The endocrinology of the menopause. *Journal of Steroid Biochemistry and Molecular Biology* 69, 31-35.

Choroszewska, A., Sawicki, W., Bentyn, K. & Strojny, P. (1989) Number and distribution of lymphocytes in epithelium of human uteri in the menstrual cycle and menopause. *Archivum Immunologiae et Therapia Experimentalis* 37, 735-739.

Conover, C.A., Faessen, G.F., IIg, K.E, Chandrasekher, Y.A., Christiansen, M., Overgaard, M.T., Oxvig, C. & Giudice, L.C. (2001) Pregnancy-associated plasma protein-a is the insulin-like growth factor binding protein-4protease secreted by human ovarian granulose and is a maker of dominant follicle selection by human ovarian granulose cells and is a maker of dominant follicle selection and the corpus luteum. *Endocrinology* 142, 2155.

Crofton, P.M., Evans, A.E., Groome, N.P., Taylor, M.R., Holland, C.V. & Kelnar, C.J. (2002) Dimeric inhibins in girls from birth to adulthood: relationship with age, pubertal stage, FSH and oestradiol. *Clinical Endocrinology* 56, 223-230.

Crow, J., Wilkins, M., Howe, S., More, L. & Helliwell, P. (1991) Mast cells in the female genital tract. *International Journal of Gynecological Pathology* 10, 230-237.

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

Davanger, S., Hjelle, O.P., Babaie, E., Larsson, L., Hougaard, D., Storm- Mathisen, J. & Ottersen, O.P. (1994) Colocalization of gamma-aminobutyrate and gastrin in the rat antrum: immunocytochemical and in situ hybridization. *Gastroenterology* 107, 137-148.

Dixon, J.S., Gosling, J.A. & Ramsdale, D.R. (1973) Urethral chromaffin cells: a light and electron microscopic study. *Z Zellforsh* 138,397-406.

Donnez, J., Casanas-Roux, F., Caprasse, J., Ferin, J. & Thomas, K. (1985) Cyclic changes in ciliation, cell height, and mitotic activity in human tubal epithelium during reproductive life. *Fertility and Sterility* 43, 554-559.

Fetissof, F., Berger, G., Dubois, M.P., Arbeille-Brassart, B., Lansac, J., Sam-Giao, M. & Jobard, P. (1985) Endocrine cells in the female genital tract. *Histopathology* 9, 133-145.

Findlay, J.K., Drummond, A.E., Dyson, M., Baillie, A.J., Robertson, D.M. & Etheir, J.F. (2001) Production and action of inhibin and activin during folliculogenesis in the rat. *Molecular Cell Endocrinology* 180,139-144.

Finn, C.A. (2001) Reproductive ageing and the menopause. *International Journal of Developmental Biology* 45, 613-617.

Gosden, R.G. & Faddy, M.J. (1994) Ovarian aging, follicular depletion, and steroidogenesis. *Experimental Gerontology* 29, 265-274.

Hagiwara, H., Ohwada, N., Aoki, T. & Fujimoto, T. (1998) Langerhans cells in the human oviduct mucosa. *Italian Journal of Anatomy & Embryology* 103 (*Suppl.* 1), 253-258.

Hayashi, M., McGee, E.A., Min, G., Klein, C., Rose, U.M., van Duin, M. & Hsueh, J. (1999) Recombinant growth differentiation factor-9 (GDF-9) enhances growth and differentiation of cultured early ovarian follicles. *Endocrinology* 140, 1236-1244.

Jaatinen, R., Bondestam, J., Raivio, T., Hilden, K., Dunkel, L., Groome, N. & Ritvos, O. (2002) Activation of bone morphogenic protein signaling pathway induces inhibin beta (B)- subunit rnRNA and secreted inhibin B levels in cultured human granulose-luteal cells. *Journal of Clinical Endocrinology and Metabolism* 87, 1254-1261.

Judd, H.L. & Fournet, N. (1994) Changes of ovarian hormonal function with aging. *Experimental Gerontology* 29, 285-298.

Koshiyama, M., Yoshida, M., Takemura, M., Yura, Y., Matsushita, K., Hayashi, M., Tauchi, K., Konishi, I. & Mori, T. (1996) Immunohistochemical analysis and distribution of oestrogen receptors and progesterone receptors in the postmenopausal endometrium. *Acta Obstetirca et Gynecologica Scandinavica* 75, 702-706.

Kyo, S., Takakura, M., Kohama, T. & Inoue, M. (1997) Telomerse activity in human endometrium. *Cancer Research* 57, 610-614.

Larsson, L.I. (2000) Developmental biology of gastrin and somatostatin cells in the antropyloric mucosa of the stomach. *Microscopy Research and Technique* 48, 272-281.

Leeson, T.S., Leeson, C.R. & Paparo A.A. (1988) *Text/Atlas of Histology*. W.B. Saunders Company. Harcourt Brace Jovanovich, *Inc.* pp 598-632.

Leone, M., Costantini, C., Gallo, G., Voci, A., Massajoli, M., Messeni Leone, M. & de Cecco, L. *(1993)* role of growth factors in the human endometrium during aging. *Maturitas* 16, 31-38.

Liverro, G., Perlino, E., Maiorano, E., Cormio, G., Ricco, R., Marra, E., Nappi, L., Giannini, T. & Selvaggi, L. (1999) TGF-beta I and IGF-I expression in atrophic postmenopausal endometrium. *Maturutas* 31, 179-184.

Matzuk, M.M. *(*2000) Revelations of ovarian follicle biology from gene knockout mice. *Molecular Cell Endocrinology* 163, 61-66.

Messinis, I.E. (2000) Ovarian regulators of gonadotropin secretion. *Annals of New York Academy of Sciences* 900, 10-15.

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

McGrath, S.A., Esquela, A.F. & Lee, S.L (1995) Oocyte-specific expression of growth/differentiation factor-9. *Molecular Endocrinology* 9,131-136.

McNatty, K., Hudson, N., Whiting, L., Reader, K., Lun, S., Western, A., Heath, D., Smith, P., Moore, L. & Juengel, J. (2007) The effects of immunizing sheep with different BMP15 or GDF9 peptide sequences on ovarian follicular activity and ovulation rate. *Biology & Reproduction* 76, 552-560.

Milne, S.A., Rakhyoot, A., Drudy, T.A., Brechin, S., Riley, S.C. & Critchley, H.O. (2001) Colocalization of matrix metalloproteinase-I and mast cell tryptase in the human uterus. *Molecular Human Reproduction* 7, 559-565.

Moore, K.L. (1988) *The Developing Human.* W.B. Saunder Company. Harcourt Brace Jovanovich, Inc. pp. 13-27.

Mori, A., Zhai, T.L., Toki, T., Nikaido, T. & Fujii, S. (1997) Distribution and heterogeneity of mast cells in human uterus. *Human Reproduction* 12, 368-372.

Nicks, K.M., Fowler, T.W., Akel, N.S., Perrien, D.S., Suva, L.J. & Gaddy, D. (2010) Bone turnover across the menopause transition: the role of gonadal inhibins. *Annals of New York Academy of Science* 192,153-160.

Nielsen, M., Bogh, I.B., Schmidt, M. & Greve, T. (2001) Immunohistochemical localization of oestrogen receptor-alpha in sex ducts and gonads of newborn piglets. *Histochemistry and Cell Biology* 115,521-526.

Noe, M., Kunz, G., Herbertz, M., Mall, G. & Leyendecker, G. (1999) The cyclic pattern of the immunocytochemical expression of oestrogen and progesterone receptors in human myometrial and endometrial layers: characterization of the endometrial-suendometrial unit. *Human Reproduction* 14, 190-197.

Overlie, I., Morkrid, L., Andersson, A.M., Skakkebaek, N.E., Moen, M.H. & Holte, A. (2005). Inhibin A and B as biomarkers of menopause: a five-year prospective longitudinal study of hormonal changes during the menopausal transition. *Acta Obstetrica et Gynaecologica Scandinavica* 84,281-285.

Palter, S.F., Mulayim, N., Senturk, L., Arici, A. (2001) Interleukin-8 in the human fallopian tube. *Journal of Clinical Endocrinology & Metabolism* 86, 2660-2667.

Pandit, L. & Ouslander, J.G. (1997) Postmenopausal vaginal atrophy and atrophic vaginitis. *American Journal of Medical Sciences* 314, 228-231.

Prior, J.C. (2002) The ageing female reproductive axis II: ovulatory changes with perimenopause. *Norvatis Foundation Symposia* 242,172-186.

Ribatti, D., Crivellato, E., Candussio, L., Nico, B., Vacca, A., Roncali, L. & Dammacco, F. (2001) Mast cells and their secretory granules are angiogenic in the chick embryo chorioallantoic membrane. *Clinical Experimental Allergy* 31, 602-608.

Richardson, S.J. (1993) The biological basis of the menopause. *Bailliers Clinical Endocrinology and Metabolism* 7,1-6.

Santoro, N. & Randolph, J.F. Jr. (2011) Reproductive hormones and the menopause transition. *Obstetrics Gynecology Clinics of North America* 38, 455-466.

Sauer, M.V., Paulson, R.J. & Lobo, R.A. (1993) Pregnancy after 50: application of oocyte donation to women after natural menopause. *Lancet* 341, 321-323.

Seifer, D.B., Scott, R.T., Bergh, P.A., Abrogast, L.L., Friedman, C.I., Mack, C.K. & Danforth, D.R. (1999) Women with declining ovarian reserve may demonstrate a decrease in day 3 serum inhibin B before a rise in day 3 follicle-stimulating hormone. *Fertility and Sterility* 72, 63- 65.

Skaper,S.D., Pollock, M. & Facci, L. (2001) Mast cells differentially express and release active high molecular weight neurotropins. *Molecular Brain Research* 97,177-185.

Doi: http://dx.doi.org/10.4314/thrb.v15i2.4

Sowers, M.R., Eyvazzadeh, A.D., McConnell, D., Yosef, M., Jannausch, M.L., Zhang, D., Harlow, S., Randolph, J.F. (2008) Anti-Mullerian hormone and inhibin B in the definition of ovarian aging and the menopause transition. *Journal of Clinical Endocrinology & Metabolism* 93, 3478-3483.

Su, Y., Wu, X., O,Brien, M., Pendola, F., Denegre, J., Matzuk, M. & Eppig, J. (2004) Synergistic roles of BMP 15 and GDF9 in the development and function of the oocyte-cumulus cell complex in mice: genetic evidence for an oocyte-granulosa cell regulatory loop. *Developmental Biology* 276, 64-73.

Welt, C.K. & Schneyer, A.L. (2001) Differential regulation of inhibin B and Inhibin A by follicle-stimulating hormone and local growth factors in human granulose cells from small antral follicles. *Journal of Clinical Metabolism* 86,330-336.

White, H.D., Yeaman, G.R., Givan, A.L. & Wira, C.R. (1997) Mucosal immunity in the human reproductive tract: cytotoxic T lymphocyte function in the cervix and vagina of premenopausal and postmenopausal women. *American Journal of Reproductive Immunology* 37, 30-38.

WHO (1996) *Research on the Menopause in the 90s.* World Health Organization Technical Report Series 866, Geneva, Switzerland.

Zalud, I., Conway, C., Schulman, H. & Trinca, D. (1993) Endometrial and myometrial thickness and uterine blood flow in postmenopausal women: the influence of hormonal replacement therapy and age. *Journal of Ultrasound Medicine* 12, 737-741.