Recent Research About the Immune Cells in the Ovary

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Abstract

The ovary is a unique female reproductive organ, and its physiological processes include follicle development, maturation, ovulation, luteinization, and closure. The ovaries contain various types of immune cells, such as macrophages, neutrophils, lymphocytes, NK cells, eosinophils, and mast cells. These immune cells play various roles in different physiological processes in the ovaries. Without the immune cells in the environment, ovarian physiological processes cannot proceed normally and orderly. For example, macrophages play a key role in maintaining ovarian vascular integrity and undergo positional migration and quantitative changes throughout the menstrual cycle. Mast cells can facilitate follicle development. In this paper, we reviewed the immune cells in the ovaries and their roles in ovarian physiology to offer additional insights into understanding the physiological functions of the ovaries from an immune perspective. This information is also important for explaining the etiology of ovarian diseases of unknown cause and the related immunotherapy.

Keywords

Ovary, immune cells, macrophages, lymphocytes, NK cells

1. Introduction

The ovary is a unique female reproductive organ in which ovarian physiological processes are carried out. Here the follicles gradually develop and mature for ovulation. The corpus luteum forms right after ovulation and is maintained for some days and then dissolves. Most follicles fail to develop and mature producing atresia. These processes cannot be carried out in a normal and orderly manner without the regulation of the immune environment within the ovary. The follicles develop in the ovary and can be divided into primordial, primary, secondary, and mature follicles based on their morphology and function. The primary follicle, usually formed by primary oocytes surrounded by granulosa cells, is the reproductive unit and demonstrates the abundance of ovarian reserve [1]. It determines the fertility and reproductive life span of the female [2]. Follicular activation in mammals occurs when the primary follicle is evolved from primordial follicles when the oocyte grows rapidly and the surrounding granulosa cells become cuboidal and proliferate [3]. During this process, some of the follicle's own components, such as zona pellucida [5], oocytes, granulosa cells [6], etc., are also susceptible to become antigens for autoimmune attack. At the same time, immune cells in the ovary undergo a directed migration in preparation for further follicular development and subsequent ovulation. The further developed follicular membrane also contains angiogenesis and immune-related cells and factors, which are essential for maintaining the structural completeness and the immune tolerance of the follicle [4].
Depending on the mutual regulation of immune cells and the cytokines they secrete, the ovary can maintain its normal physiological function without developing autoimmune diseases. When follicles develop, the vast majority of follicles do not ovulate and enter a degenerative process called follicular atresia [7], a series of immune cells are gathered in the follicle to promote apoptosis at this time. Liu Z and Smolikova found that ovulation is the expulsion of mature oocytes from the follicle and exhibits inflammatory properties because of the immune mediators involved [8, 9]. It is clear that a team of immune cells and cytokines lays the foundation for the ovarian immune environment, which provides a guarantee for the normal conduct of physiological processes in the ovary. In this article, we will describe some of the immune cells and cytokines in the ovary and discuss how they collaborate with each other to maintain normal ovarian function.

2. Function and localization of immune cells in the ovary

A variety of immune cells are present in the ovary, including macrophages, neutrophils, lymphocytes, eosinophils, and mast cells. The functions and localization of the above immune cells in the ovary will be described in detail below.

2.1 Macrophages

Macrophages are widely present in female reproductive tissues [10] and it is the highest percentage of immune cells in the ovary [11]. According to their origin, tissue-resident macrophages can be divided into blood monocyte-derived macrophages and locally self-renewing resident macrophages [10]. Macrophages are divided into two categories according to their function: M1 and M2. M1 macrophages are mainly induced by Th1 signaling, such as lipopolysaccharide (LPS) and gamma-interferon (IFN-γ). They also express high levels of inflammatory cytokines, including tumor necrosis factor-alpha (TNFα), interleukin (IL)-6, and IL-1β. They help the host kill bacteria and viruses in time to avoid infection [12]. M2 macrophages are induced by Th2 signaling, such as IL-4 and IL-13, and make a difference in eliminating inflammation and infection as well as promoting wound healing and tissue remodeling [13]. Macrophages are present in the ovarian medulla, theca layer, follicular fluid, and corpus luteum [14-17].

Macrophages play a key role in maintaining ovarian vascular integrity. Turner et al. [18] injected diphtheria toxin (DT) to specifically ablate ovarian macrophages in adult women and found that as macrophage ablation progressed, increased ovarian hemorrhage with significant endothelial cell depletion was observed in luteal and thecal tissue. This phenomenon may result from enhanced collagen III catabolism and angiogenic factor deficiency due to the relative downregulation of tissue inhibitors of metalloproteinases (TIMPs) [19].

The current study found that macrophages promote follicular development. Yosuke et al. [20] used mice that can be selectively depleted of M1 or M2 macrophages and found that M1 macrophages or dendritic cells may participate in folliculogenesis, whereas M2 macrophages do not work on follicle formation. Fukumatsu et al. [21] in an earlier study found that culturing rat granulocytes and peritoneal macrophages together allows granulocytes to proliferate. Subsequent studies found that growth factors secreted by macrophages can affect ovarian function through autocrine or paracrine secretion [22]. For example, fibroblast growth factor (bFGF) can affect follicle development [23] and prevent granulosa cells from spontaneous apoptosis in culture [24, 25].

Macrophages can also promote ovulation. During ovulation, macrophages are able to release important cytokines that promote ovulation, such as IL-1b [26], TNFα [27], and several protein hydrolases, such as matrix metalloproteinases (MMPs) [28]. The follicle is known to produce proteases that act on the basement membrane and follicular wall to degrade them in order to ovulate. Butler [29] found that ovulation was inhibited in rats in which tissue collagenase and related metalloproteinases are inhibited.

Macrophages are also involved in follicular atresia and luteolysis. Studies in guinea pigs, rabbits, and human ovaries have shown that macrophages can phagocytose apoptotic follicular epithelial cells, atretic granulosa cells, and apoptotic luteolysis cells [30, 31].

Current studies on macrophages have also revealed that macrophages undergo positional migration and quantitative changes with the menstrual cycle. Brannstrom found that the migration of macrophages increased in the theca layer of human follicles before ovulation [32]. Ruijin Wu et al. [16] showed that changes in macrophage numbers correspond to the function of the human menstrual corpus luteum, with an increase in the early phase, relatively constant in the middle phase, and a decrease in the late phase. However, another study showed that [33] the number of macrophages tended to increase from the early to late luteal phase, suggesting that macrophages have a pro-luteinizing effect in early and mid-luteal period and a pro-luteal lysis effect in late luteal period. The changes in macrophages in luteal production and lysis need to be further investigated.
2.2 Neutrophils

Neutrophils are the most numerous of the peripheral blood leukocytes and are the first to arrive when inflammation occurs [34]. Neutrophils are differentiated from stem cells in the bone marrow [35], then they are released into the circulation and migrate via the endothelium to reach the tissues to exert their effects [36]. They can defend against fungal and bacterial infections, but when they are activated abnormally they produce an autoimmune response that can lead to damage to the body[37]. Studies have shown that neutrophils in the ovary are divided into peripherally imported neutrophils and resident neutrophils [38]. However, neutrophils are less abundant in healthy ovaries [39, 40]. Neutrophil phenotype is determined by surface markers and receptors as well as chemokines to different cytokines [34]. The "polarization of neutrophil phenotype", similar to that of monocytes/macrophages, was proposed by Fridlender et al. to classify neutrophils into inflammatory (N1) and anti-inflammatory (N2) [41]. However, studies on these two phenotypes of neutrophils in the ovary are lacking. Neutrophils are found in the medulla, theca layer and corpus luteum [14, 15, 42].

Neutrophils have ovulation-promoting effects in rats. Brannstrom et al. [43] found that ovulation rates were reduced by 27% in rats given a monoclonal antibody against neutrophils to ablate peripheral blood neutrophils. Ujioka's experiment [44] also showed that neutropenia reduced ovulation rate, further demonstrating the ovulation-promoting effect of neutrophils. Noel et al. [45] found that serum G-CSF levels peaked during gonadotropin stimulation of the ovaries to induce spontaneous ovulation. Granulocyte colony-stimulating factor (G-CSF) is a major factor determining how neutrophil life activity proceeds [35]. This result suggests that neutrophil promotion of oocyte maturation and subsequent ovulation may be regulated by G-CSF.

Neutrophils have dual regulation of luteal production and lysis. Recent studies have shown that neutrophils and interleukin-8 (IL-8), a neutrophil chemoattractant that accumulates neutrophils within the corpus luteum, were found to promote luteal development by promoting angiogenesis [46] in both bovine and human corpus luteum. The former is directly infiltrated by neutrophils [47] and the latter involves IL-8 secretion via endothelial cell feedforward paracrine [48]. What’s more, the rapid accumulation of polymorphonuclear neutrophils in the corpus luteum during prostaglandin F(2α)-induced lysis of the bovine corpus luteum suggests that the large accumulation of neutrophils promotes lysis of the corpus luteum [49].

During the menstrual cycle, significant fluctuations take place in the number of neutrophils. Brännström’s [50] studies on rat ovaries have shown that neutrophil density increased 3-fold in the medullary layer and 8-fold in the cortical zone during ovulation. The proportion of leukocytes in the medullary zone in the total number was smaller throughout the menstrual cycle. Subsequently, Brännström [32] and Noël et al. [45] also found neutrophil density increased remarkably in the thecal layer during ovulation and that IL-8 and Cytokine-induced neutrophil chemoattractant (CINC/gro) expression were responsible for this accumulation [51]. Also, the corpus luteum was rich in neutrophils [32].

2.3 Lymphocytes

Lymphocytes are the core of the immune response and can be divided into three categories: B cells, T cells, and NK cells, depending on their origin, morphological structure, surface markers, and immune function. Bone marrow-derived B lymphocytes can be further developed into plasma cells, and thymus-derived T lymphocytes are further divided into helper T cells (Th), regulatory T cells (Treg), and cytotoxic T lymphocytes (CTL). NK cells are cytotoxic components of innate lymphoid cells (ILC) that resist viral infection and help inhibit tumor growth and metastasis [52]. Because estrogen promotes lymphocyte migration, lymphocyte immunity in the ovary exhibits characteristics that are compatible with estrogen levels [53]. Lymphocytes are found in the medulla, theca layer, follicular fluid, and corpus luteum [14, 15, 17]. The distribution and functions of several cells in the ovary are described in detail below.

2.3.1 T cells

T cells are indispensable in cellular immunity associated with host anti-transplantation response and tumor response because of their regulatory and effector functions. According to their function, T cells can be classified as helper T (Th) cells, regulatory T cells (Tregs), and cytotoxic T lymphocytes (CTL) [54].

T cells help to keep maintenance of normal ovarian immunity. Kryczek et al. [55] found that luteinized granulosa cells locally produce CXCL12, and recruit T lymphocytes in coordination with local lymphocytes for greater granulocyte survival and improved embryo quality. T lymphocytes also secrete a range of cytokines such as IL-2, IL-6, GM-CSF, and IFN, all of which are implicated in ovarian physiology [17]. T cells also promote luteal secretion.
Emi et al. [56] found that when human granulosa luteal cells were cultured with autologous or allogeneic peripheral blood lymphocytes, luteinizing granulosa cells produced more progesterone.

Studies on rat ovaries have shown that before ovulation, T lymphocytes were present in large numbers in the medullary region of the ovary and in small numbers in the thecal layer, with no significant change in density either before or during ovulation, followed by a significant increase in T lymphocyte density in the medullary region of the lutealized ovary [50]. Studies on human ovaries have shown that all subtypes of T lymphocytes can be detected in the ovary [57]. Before ovulation, T lymphocytes were present in the interfollicular cortical stroma, and they were significantly increased in the atretic follicles. After ovulation, they were mainly distributed in the central lumen of corpus luteum and keep a quantitative increase in the development of the corpus luteum [57, 58]. The specific roles of T lymphocyte subtypes in the ovary are described below.

1) Helper T cell (Th)

Helper T cells are regulated by different cytokines and can be subdivided into subpopulations such as Th1, Th2, and Th17. Th cells exert the immune effect by controlling cellular and humoral immunity [59]. Th1 is induced by interleukin-12 (IL-12) and gamma interferon (IFN-γ) and produces IFN-γ, which stimulates macrophages, resulting in immune cell-mediated destruction [60]. Th2 is induced to differentiate by IL-4 and secretes IL-4, IL-5, and IL-13, which stimulate B cells and lead to humoral immune responses [60]. Th17 was discovered in 2005 [61] and is induced by IL-6, IL-21, IL-23 and TGF-β [62].

Th1 cells antagonize Th2 cells [63, 64]. Th1 cytokines have been recognized to enhance ovulation in rats [65], and the synergistic effect of Th1 cytokines also causes some somatic changes that enhance ovulation [66]. The defective production of Th2 cytokines may contribute to unexplained recurrent abortions [67]. However, when self-regulation disorders, the Th1 T-cell response can target self-peptides and lead to a variety of autoimmune diseases [62]. The Th1 T-cell machinery has been shown to be an important pathway in autoimmune ovarian inflammation [68]. Th1/Th2 abnormalities are an important indicator of immune dysregulation and are currently being investigated in polycystic ovary syndrome (PCOS) [69], premature ovarian failure (POF) [70], and ovarian cancer [71], with the former two showing a Th1 predominance but a significantly lower Th1/Th2 ratio in ovarian cancer. The difference may be related to the different etiologies.

The functional status of Th17 varies from non-pathogenic to pathogenic, it can produce IL-10, which has anti-inflammatory and regulatory effects, as well as pro-inflammatory factors that induce tissue inflammation and promote B-cell responses [62]. Th17/Treg is another commonly used indicator to describe whether immune imbalance is present. When the Th17/Treg ratio is upregulated, the body is in an inflammatory state in which Th17 cells are increased and dominant and Treg cells are less suppressive [72]. Currently, a significant increase in Th17/Treg was found in polycystic ovary syndrome (PCOS) [73], premature ovarian failure (POF) [74] and ovarian cancer [71].

2) Regulatory T cells (Treg)

Treg cells are thought to be responsible for suppressing the potentially harmful activity of Th cells and thus suppressing excessive immune responses [75]. Initially, they were thought to be used to maintain autoimmune tolerance [76] to prevent autoimmune diseases. Treg cells can produce suppressive cytokines such as IL-10 and TGF-β and interfere with T-cell survival through IL-2 depletion. It can also directly inhibit the maturation of antigen presenting cells and eliminate effector cells thereby inhibiting T-cell proliferation [77]. As a result, Treg cells can inhibit the maturation of antigen-presenting cells and the further differentiation of lymphocytes (T cells, B cells, NK cells) to exert their effects [78]. Treg cell studies have been performed in cervical cancer [79], recurrent miscarriage disease [80] and ovarian cancer [81], all of which resulted in upregulation and maintenance of high levels of CD4+CD25+ Treg cells.

Ovarian inflammation can be suppressed by Treg. Spontaneous ovarian autoimmune disease occurs in mice with thymus removal shortly after birth, but this can be cured by passive transfer of CD4 + CD25 + regulatory T cells (Tregs) from the spleen of normal adult mice [82].

Treg cells can also regulate the function of the corpus luteum through changes in their own numbers. Arruvi's [83] study demonstrated that Treg cells are regulated by sex hormones during the menstrual cycle. In fertile non-pregnant women, Treg cells were detected to increase during the late follicular phase of the menstrual cycle but decreased dramatically in number during the subsequent luteal phase. This change is closely correlated with serum estradiol levels. The possible mechanism for this change is that Treg cells suppress activated T lymphocytes in the early luteal phase to prevent premature luteal failure, but once the corpus luteum begins to lyse, Treg cells decline, thereby weakening their suppressive effect on T lymphocytes and allowing them to release cytokines that may cause luteal cell death.

3) Cytotoxic T lymphocytes (CTL)

Cytotoxic T cells (CTL), also called CD8+ T cells, are a subset of leukocytes. CTL are specific T cells which are
restricted by MHC class I molecules [84]. They cause cellular damage by secreting perforin to perform cytotoxic functions upon cell contact [85], which have a killing effect on tumor cells and other cells expressing the corresponding antigens, thus forming an important line of defense for the body's antiviral and antitumor immunity.

Under normal conditions CD8+ T cells promote luteolysis. Hameed et al. [86] found that CD8+ T lymphocytes and cells of the monocyte/macrophage spectrum are physiological cells that mediate inflammatory processes in the human corpus luteum and that perforin plays a role during the physiological inflammatory response to human luteolysis. CD8+ T cells also have applications in the treatment of ovarian cancer. One study [87] demonstrated that CTL can inhibit the growth of human ovarian cancer SKOV-3, and a recent study found [88] that estrogen binding to estrogen receptor β on CD8+ T cells will turn on the phosphotyrosine switch to enhance T cell receptor activation and anti-tumor immunity.

Excessive CD8+ T cells can also be damaging to the ovary. Zhao [89] showed that the immune homeostasis of follicular fluid is disrupted by abnormally elevated CD8+ T cells as well as CCL5 and IFN-γ, causing damage to granulosa cells and reduced ovarian reserve (DOR).

### 2.3.2 B cells and NK cells

B cells are usually recognized by the surface membrane immunoglobulins (sIgs) receptors or B cell-specific molecules on their cell surface [60]. Antigen-specific B cells and activated T cells have "homologous interactions" [90], which means that B cells concentrate and process the antigen and present it to the antigen-specific T cells, then T cells produce and release cytokines that stimulate the B cells to differentiate into plasma cells. Plasma cells exert immune effects by secreting immunoglobulins.

B cells play a very small role in normal ovarian function. Several studies have shown that B cells are present in very low levels in normal premenopausal ovaries [15, 50, 91]. Bukulmez has reported that immunoglobulin (Ig)G, IgA, and secretory IgA are absent in all ovarian sections [15], while Alzubaidi [92] reported that a certain amount of non-pathogenic anti-ovarian antibodies (AOAB) are present in normal women for the clearance of senescent tissue in vivo. When ovarian immunity is abnormal, B cells produce large amounts of autoimmune antibodies that bind to the relevant antigens in the ovary and produce cytotoxic effects, leading to a range of ovarian diseases [93].

### 2.3.3 NK cells

NK cells can be divided into immunomodulatory (CD56CD16+), cytotoxic (CD56CD16), and NKT (CD56CD3) subpopulations based on their function, with NK cells regulating TH1 and TH2 balance [94].

NK cells are extremely low in normal premenopausal ovaries [15, 50, 91], it has been detected in follicular fluid[94]. In the ovary, NK cells are engaged in folliculogenesis, ovulation, and menstrual cycle [95, 96] and can promote angiogenesis and oocyte development. Fainaru [97] performed ovarian stimulation on patients and (CD56CD16-) NK cells were found to cumulate in the follicular fluid of patients who responded well, suggesting that this kind of NK cells may support follicular angiogenesis and oocyte. Another of his study [98] showed that "angiogenic" (CD56+CD16-) NK cells appear in the sinus follicular period and promote follicular development, while a decrease in the "cytotoxic" (CD56+CD16+) NK cells is shown as follicles mature.

### 2.4 Eosinophils

Eosinophils are bone marrow-derived leukocytes and are usually less than 5% of blood leukocytes. Eosinophils can modulate immune and inflammatory responses locally, and parasitic infections and allergic inflammation can lead to elevated levels of eosinophils [99]. Cytokines secreted by eosinophils have been shown to be associated with the regenerative response to tissue injury [100, 101], suggesting that eosinophils may be helpful in menstruation-related tissue repair. However, studies have demonstrated that as we age, eosinophils increase the risk of chronic inflammatory disease [102]. Some cases of eosinophilic ovarian inflammation have also been reported [103, 104]. Eosinophils are less abundant in the ovary and are currently thought to be localized mainly in the medulla, thecal layer, and corpus luteum [14, 15, 17].

Eosinophils are involved in the angiogenesis of the corpus luteum as well as the post-ovulatory thecal layer. Rohm [105] found CD62P expression in the dilated vessels in the thecal layer of newly ruptured bovine follicles, and this selection is involved in the migration of eosinophils under physiological conditions. Murdoch et al. [106, 107] used different modalities to induce eosinophil reduction and all found that the corpus luteum size was reduced, the vascular bed was underdeveloped and therefore endocrine function was deficient. Degranulated eosinophils were often concentrated in areas of vascular development. This function may involve the secretory products of eosinophils, such as cationic proteins [107] and vascular endothelial growth factor (VEGF) [106]. It is now known that
Eosinophils are present in a very limited location in the ovary. Standaert’s [108] studies on the porcine preovulatory follicle (PO) and corpus luteum (CL) have shown that eosinophils are the Highest number of leukocytes in the thecal tissue of the PO and in the degenerated CL, but eosinophils were rarely observed in other stages of CL. Murdoch’s study on sheep showed that corpus luteum tissue was shown to produce specific chemotactic attractants for eosinophils[109]. Karström [110] studies in humans showed that eosinophils were rarely detected in the ovaries during any phase of the menstrual cycle. However, later Aust’s survey of human [111] found eosinophils in the developing corpus luteum for the first time and showed that in freshly ruptured follicles, eosinophils were more aggregated in the blood vessels, more adherent to the endothelium and were less frequently seen in the thecal layer of freshly ruptured follicles and newly created corpora lutea.

2.5 Mast cells

Mast cells are closely associated with the inflammatory response. Binding of estradiol and progesterone to receptors on mast cells induces mast cell degranulation and releases a range of pre-formed mediators (including proteases such as trypsin, histamine, bradykinin, proteoglycans, and heparin) and newly formed mediators (thromboxane, platelet-activating factor, leukotrienes, and prostaglandins) [96].

Mast cells can facilitate follicle development. Nakamura’s [112] study on how mast cells affect early follicular development revealed that early follicle development needs for mast cells, particularly in the process of "nest breakdown ", during which smaller cysts are divided from primitive oocytes until individual oocytes are retained. The mechanism may be that TNF-α produced by mast cell secretion comes into contact with oocytes, which compresses the cytoplasm of the oocyte, causing some oocytes to develop deformed or vacuolated structures [112]. The mediators released by mast cell degranulation also have a facilitative effect on ovulation. A retrospective study on the effects of histamine on ovarian function showed that blocking the action of histamine or depleting it, prevented increased ovarian congestion and prevented ovulation by blocking histamine-induced ovarian contraction [113]. Szukiewicz’s [114] study showed that mast cell-derived IL-8 also promotes follicle growth and ovulation.

Differences in estrous cycles make the distribution of mast cells species-specific [115]. In rodents, mast cells are observed only in the ovarian hilum and are not found in the follicles and corpus luteum [113]. Brännström [50] performed toluidine blue staining of immature follicles in rats to identify connective tissue-type mast cells and found them to be less numerous and strictly confined to the medullary region. Abdulrahman's [116] analysis of the dominant follicle in cattle showed that the first cells to flood into the follicle at ovulation were granulosa leukocytes, mainly mast cells, and mast cells infiltrated into the membranous layer of the follicle. Gamal’s [117] study on human ovaries showed that mast cells are found mainly deep in the cortices and near the blood vessels, and occasionally in the corpus luteum.

3. Conclusion

Under normal conditions, the immune environment in the ovary is in a dynamic process of change. Immune cells migrate and change their location and density at different times according to the physiological activity of the ovary while secreting the corresponding cytokines. Except the direct action on functional cells in the ovary, some of them also act on the immune cells. The interplay of immune cells and cytokines allows all physiological activities in the ovary to proceed in an orderly and efficient manner. How the precise migration of immune cells is achieved and how the regulation of cytokine secretion is achieved needs to be further investigated. Studies on the ovarian immune environment are currently based on animal experiments, but less on the human ovary, and further validation is needed to determine whether the two can be effectively linked.

Currently, many ovarian diseases of unknown cause may be associated with dysregulation of the ovarian immune environment, and understanding the normal ovarian immune environment is important for the study of the etiology, as well as for guidance and reference in the immunotherapy associated with ovarian diseases known to be caused by immune factors.

Funding

This work was supported by the Independent Innovation Fund of HUST (5003519019) and the Ministry of Education Industry Education Collaborative Education Project (220601164013611).

DOI: 10.26855/ijcemr.2024.04.024
Competing Interests

The authors declare that there is no conflict of interests.

Availability of data and materials

Because this is a review, data sharing of findings by others may not be applicable for many sections as no datasets were generated or analyzed during the writing of this review.

Authors’ contributions

ST C, QL L wrote the article and performed all of the necessary literature searches and data compilation. CX Z, XH L, JX Z, and SY Z performed the necessary literature searches and data compilation. DH H and H Z designed the review, reviewed it, and approved the submitted manuscript. All authors have read and approved the final manuscript.

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Evidence that polymorphonuclear neutrophils infiltrate into the developing corpus luteum and promote

DOI: 10.26855/ijcemr.2024.04.024


