International Journal of Medicine and Medical Research
2022, Volume 8, Issue 1, p. 37-43

DOI 10.11603/ijmmr.2413-6077.2022.1.13083

AN OBSERVATIONAL STUDY TO FIND RELATIONSHIP OF ACUTE APPENDICITIS TO MENSTRUATION CYCLE IN NORTHERN AND NORTHEASTERN PART OF INDIA

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Background. *Diagnosing acute appendicitis correctly in a female patient is a challenge for a practicing surgeon. Rate of misdiagnosis of acute appendicitis is very high among female patients. There are many studies carried out to find incidence of acute appendicitis as per various phases of menstruation cycle but the results were conflicting.*

Objective. *The study was conducted to find the relationship of acute appendicitis with the different phases of the menstruation cycle.*

Methods. *This research was an observational study carried out in two regional hospitals in northern and north-eastern part of India. Duration of study was 24 months between 01 June 2019 and 31 May 2021. Inclusion Criteria were for all female patients, non-pregnant and menstruating, who were histopathologically confirmed as acute appendicitis. All pathologically proven negative appendectomy patients were excluded from this study. All female patients taking oral contraceptive pills (OCP) were excluded from the study.*

Results. *A total of 96 females were hospitalized in both hospitals during the study period; 12 of them did not attain menarche (12.5%), 6 had menopause (6.3%) and 78 were menstruating (81.25%). Of those 78 patients, who had physiological menstrual cycles, 6 were in menstrual phase (7.6%), 18 were in proliferative phase (23%), and 54 in luteal phase (69.2%). In our study, there were only 6 cases of acute appendicitis during menstruation. therefore, the expected ratio of cases was 6/14=0.42. The corresponding expected rate for the proliferative phase was 2.78×9=25 cases, whereas for the luteal phase it was 2.78×14=38.92. The expected ratio was 18/25=0.72 for the proliferative phase and 54/39=1.38 for the luteal phase. There was a significant increase in number of cases of acute appendicitis among the menstruating women in luteal phase with p value <0.05. Mean age of the study participants was 28.31±9.56.*

Conclusions. *According to the result of the study, the incidence of acute appendicitis significantly differs in different phases of menstruation cycle with highest incidence in luteal phase. Hence, female hormones (estrogen and progesterone) are significant in causing acute appendicitis.*

KEYWORDS: acute appendicitis; menstruation phase; proliferative phase; luteal phase.

Introduction

Diagnosing an acute appendicitis in female patients is a challenge for a practicing surgeon. The rate of misdiagnosis is comparatively high in female patients especially in reproductive age group. The lifetime risk of appendicitis is 6.7% for females [1]. Diseases of the female internal reproductive organs that may erroneously be diagnosed as appendicitis in approximately descending order of frequency include pelvic inflammatory disease, ruptured graffian follicle, twisted ovarian cyst or tumor, endometriosis and ruptured ectopic pregnancy [1]. Timely diagnosis and early treatment can prevent complications associated with the disease. The sonographic diagnosis of acute appendicitis has reported sensitivity of 55% to 96% and a specificity of 85% to 98% [1]. Appendicitis is also associated with gastrointestinal symptoms like nausea (sensitivity, 58%; specificity, 36%), vomiting (sensitivity, 51%; specificity, 45%), and anorexia (sensitivity, 68%; specificity, 36%) [1]. Gastrointestinal symptoms that develop before the onset of pain suggest a different etiology such as gastroenteritis [1].

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The ratio of cases of appendicitis to cases of pelvic inflammatory disease is low in females in the early phase of the menstrual cycle and high during the luteal phase [1]. Many studies showed different results. Arnbjo rnsson et al. showed that appendicitis is more common during the luteal phase of the cycle [2] whereas Robinson et. al. showed that acute appendicitis is equally common in all phases of the cycle [3]. The aim of the current study was to find out the relationship of acute appendicitis to menstruation cycle.

Methods

This study was an observational study carried out in two regional hospitals in northern and north-eastern parts of India. The study was aimed to assess the relationship of phases of menstruation cycle to acute appendicitis. Duration of study was 24 months between 01 June 2019 and 31 May 2021.

Inclusion Criteria: all female patients, non-pregnant and menstruating, who were histopathologically confirmed as acute appendicitis.

Exclusion Criteria: all pathologically proven negative appendectomy patients were excluded from this study. All female patients, who were consuming in OCP, were excluded from the study.

Menstrual cycle was divided into 3 phases:

1. Menstruation phase; 2. Proliferative phase; 3. Luteal phase.

Duration of two phases was considered as constant (a) menstruation phase: 05 days of menstruation in physiological cycle from the beginning of bleed; (b) luteal phase: last 14 days of cycle (calculated retrospectively 14 days from the first day of menstruation bleed of next cycle excluding the day 1 of bleed). Hence, the period of proliferative phase was variable. It was also considered that ovulation occurred at the 14th day of the cycle.

Results

A total of 96 females were hospitalized in both hospitals during the study period (Table 1); 12 of them did not attained menarche (12.5%), 06 had menopause (6.3%), and 78 were menstruating (81.25%). Of those seventy-eight patients, who had physiological menstrual cycles, 6 were in menstrual phase (7.6%), 18 were in proliferative phase (23%), and 54 – in luteal phase (69.2%).

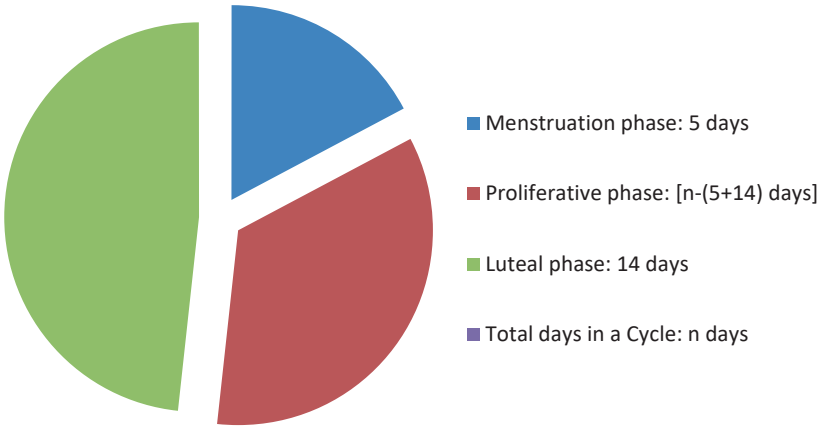

Fig. 1. Phases of menstruation cycle.

Table 1. Acute appendicitis cases (total number and percentage) as per phases of menstruation

	Number of females	Percent
Not attained menarche	12	12.5
Menstrual phase	6	6.3
Proliferative phase	18	18.8
Luteal phase	54	56.3
Post menopause	6	6.3
Total	96	100.0

Four out of seventy-eight acute appendicitis cases (Table 2) in menstruating females were complicated type, whereas none in non-menstruating female group had any complications.

The expected daily occurrence of acute appendicitis for patients with physiological menstrual cycles (for a 28-day cycle) would have been 78/28 = 2.78 cases/day. The expected rate for cases of acute appendicitis during menstruation (accepting that menstruation lasts for 5 days), would have been 2.78×5=14 cases. In current study there were only 06 cases of acute appendicitis during menstruation. The observed: expected ratio of cases therefore was 06/14=0.42. The corresponding expected rate for the proliferative phase was 2.78×9=25 cases, whereas for the luteal phase it was 2.78×14=38.92. The observed: expected ratio therefore was 18/25=0.72 for the proliferative phase and 54/39=1.38 for the luteal phase.

There was a significant increase in number of cases of acute appendicitis among the menstruating women in luteal phase with p value <0.05.

The mean age of the study participants was 28.31±9.56.

Table 2. Total complicated and non-complicated cases

	Menstruating	Non Menstruating	Total
Complicated	4	0	4
Non Complicated	74	18	92
Total	78	18	96

Table 3. Observed frequency, expected frequency and P value with respect to different phases of menstruation cycle

Phase of menstrual cycle	Observed frequency	Expected frequency	P value
Menstrual	6	14	P value 0.034066
Proliferative	18	25	
Luteal	54	39	
Chi-square statistic 6.7589			

Table 4. Mean, Median, Std deviation and Ranges

Statistics		
N	Valid	78
Mean		28.31
Median		28.00
Std. Deviation		9.558
Range		39
Minimum		13
Maximum		52

Discussion

The previous studies by Arnbjornsson [2] and Eldar et. al. [4] reported that incidence of histologically confirmed acute appendicitis was less common during menstruation phase [1] but the difference were not statistically significant. On literature search before these current studies, there were conflicting observations. Some studies [1, 4] showed higher incidence of acute appendicitis in luteal phase whereas some other [2] – in proliferative and menstruation phase. Another study by Robinson et. al. failed to show any difference [3].

The study had established that there was a significant increase in number of cases of acute appendicitis among the menstruating women in luteal phase with p value <0.05. Similar result was shown in the studies by Eldar et. al. The cause of this significant raise in incidence of acute appendicitis may be because of low estrogen level and high progesterone level modulating immune response and increasing susceptibility for gut infections.

Souza et. al. [5] reported increased NK activity in follicular phase as compared with luteal phase. Progesterone receptors and progesterone induced apoptosis of NK cells and suppresses IL-12-induced IFN-g production of Killer Ig-like receptor (KIR)+ NK cells [6]. Whereas estrogen has been reported in many studies to prevent B cell apoptosis, enhance survival and activation of autoreactive cells [7], and increase expression of CD4+ T cell chemokine receptors [8]. Estrogen exerts immune regulation via estrogen receptors (ERs) on the lymphocytes, and receptors for estrogen, progesterone, androgen, and glucocorticoid are found in lymphoid organs and/or lymphocytes [9, 10].

Hall et. al described that concentrations of progesterone fluctuated over the life course in females, with increased concentrations at puberty, cyclical changes during the menstrual cycle, and a steady rise during pregnancy followed by a sharp decline post-partum [11]. At menopause, concentrations steadily declined to levels that are similar to those prior to puberty [11].

Progesterone hormone level started rising after ovulation on the 14th day of cycle and reached its highest level during mid-luteal phase (Fig. 2). Speroff et al. in his study mentioned that serum levels of progesterone fluctuate during the menstrual cycle with a peak of 20 ng ml^{-1} during the luteal phase and the nadir (<1ng ml^{-1}) during the follicular phase [12].

Progesterone generally inhibits inflammatory innate immune responses [11]. In vitro studies by Hardy et. al. and Jones et. al. showed that progesterone can suppress activation of macrophages and dendritic cells [13, 14]. When progesterone is bound to its receptor, it directly interferes with the transcription factor nuclear factor-kappa B (NF-kB) through transrepression and inhibits gene transcription downstream of the NF-kB pathway, including cyclooxygenase-2 to decrease inflammation [13, 15]. Progesterone can also decrease inflammation by inhibiting the production of proinflammatory cytokines (e.g., TNF-a, IFN-g, and IL-12) and increasing production of anti-inflammatory cytokines, including IL-10 [14, 16].

Raised level of progesterone also suppresses Th1 response and enhances IL-10 producing Th2 cells. Miyaura et. al. in his study mentioned that progesterone was established to suppress Th1 response and enhance IL-10 producing Th2 cells [17]. Ehring et. at. in his study had showed that progesterone suppressed immune functions of T cells by a non-genomic mechanism, which was the blocking of K^+ channel, Ca^{2+} signaling and NF of activated T cells driven gene expression [18]. Siiteri et. al. had demonstrated in vivo the immunosuppressive effects of progesterone in his study by prolonged survival of xenografts near silastic implants containing progesterone at concentrations typically found in the placenta [19]. Hence, such high progesterone level in luteal phase may have caused unfavorable immunity changes leading to more susceptibility to gut infection and causing highest incidence of acute appendicitis in luteal phase.

Estrogen hormone increases its level from menstruation phase and reaches its peak at late proliferative phase. Estrogen then decline its level and reaches minimum level at late luteal phase. Hence, maximum proliferation of both lymphocytes and macrophages occurs during proliferative phase whereas minimum proliferation of both lymphocytes and macrophages occurs during luteal phase.

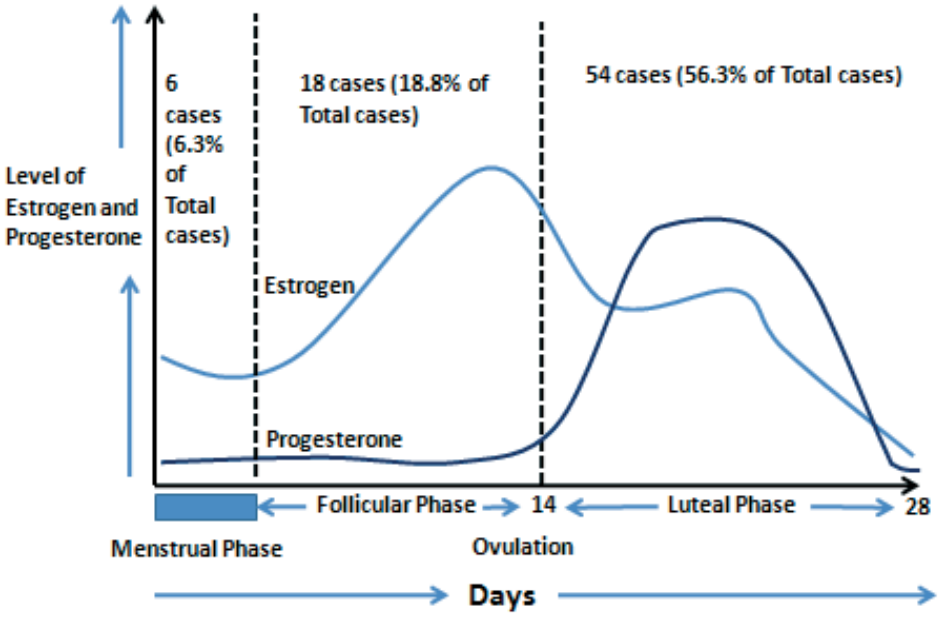

Fig. 2. Relationship between different level of estrogen and progesterone with percentage of acute appendicitis in different phases of menstruation cycle.

Whitacre et. al. stated in his study that the effects of estrogen were pleotropic on immune cell function and estrogen had been shown to significantly stimulate the proliferation of both lymphocytes and macrophages [20]. In many studies, estrogen has been shown to regulate immune response by impairing negative selection of high affinity auto-reactive B cells, modulating B cell function and leading to Th2 response [21, 22]. Estrogen also influences physiological functions via ERs which are expressed in brain, gut epithelial cells, lymphoid tissue cells as well as immune cells [23, 24]. R. Mo et. al has stated that estrogen also induces T cell homing by enhancing the expression of C-C chemokine receptor type 5 (CCR5), a homing marker [8]. Many studies has also shown that estrogen regulates immune response via modulation of endosomal TLRs and TLR8 expression thus hormonal balance determines the overall response to infection in females [25, 26, 27]. Hence, such low estrogen level with high progesterone level in luteal phase may cause unfavorable immunity changes leading to more susceptibility to gut infection and causing highest incidence of acute appendicitis in luteal phase and vice versa in proliferative phase.

Conclusions

According to the results of the study, it can be concluded that the incidence of acute appendicitis significantly differs in different phases of menstruation cycle with highest incidence in luteal phase. Hence, female hormones (estrogen and progesterone) are significant in causing acute appendicitis. This relationship can be used as additional guiding tool or information when there is diagnostic dilemma for acute appendicitis in females.

Limitations

Small sample size.

Conflict of Interests

Authors declare no conflict of interest.

Acknowledgements

I express thanks to all my interns Mr. Rameez, Mr. Praveen, Mr. Suryakant, Mr. Ashok, Mr. Sryakant and Mr. Agyastha for helping me in collection of data, tabulation and statistical analysis.

Author's Contributions

Thokchom Bishwajit Singh, Ranjan Kumar – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Ankur Nigam* – investigation, formal analysis; *Tekcham Roshini Devi* – data curation, writing – reviewing and editing.

ВЗАЄМОЗВ'ЯЗОК ГОСТРОГО АПЕНДИЦИТУ ТА ТА ФАЗИ МЕНСТРУАЛЬНОГО ЦИКЛУ У ЖИТЕЛІВ ПІВНІЧНОЇ ТА ПІВНІЧНО-СХІДНОЇ ЧАСТИНИ ІНДІЇ

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Вступ. *Діагностування гострого апендициту у пацієнта може бути проблемною для практикуючого хірурга. Частота неправильної діагностики гострого апендициту дуже висока серед пацієнтів. Існує багато досліджень, проведених для виявлення частоти гострого апендициту відповідно до різних фаз циклу менструації, але їх результати є суперечливими.*

Мета. *Дане дослідження проводилося для встановлення та оцінки взаємозв'язку гострого апендициту з різними фазами менструального циклу.*

Методи. *Дослідження було спостережним, проведеним у двох регіональних лікарнях у північній та північно-східній частині Індії. Тривалість дослідження становила 24 місяці з 01 червня 2019 року по 31 травня 2021 року. Критерії включення: Усі пацієнти, які не порушень менструального циклу та які мали гістопатологічне підтвердження діагнозу гострий апендицит. Критерії виключення: Усі пацієнти яким не проводилася апендектомія чи які приймали оральні контрацептиви, були виключені з дослідження.*

Результати. *Всього 96 жінок були госпіталізовані в обох лікарнях протягом періоду дослідження. З них 12 не досягли менархе (12,5%), 6 мали менопаузу (6,3%), а 78 – мали менструальні цикли (81,25%). З тих 78 пацієнтів, які мали фізіологічні менструальні цикли; 6 були в менструальній фазі (7,6%), 18 - у*

проліферативній фазі (23%) та 54 у лютеїновій фазі (69,2%). У нашому дослідженні під час менструації було лише 6 випадків гострого апендициту. Таким чином, спостережуване: очікуване співвідношення випадків становило 6/14 = 0,42. Відповідна очікувана цифра для проліферативної фази становила 2,78×9 = 25 випадків, тоді як для лютеїнової фази було 2,78×14 = 38,92. Таким чином, спостережуване/очікуване співвідношення становило 18/25 = 0,72 для проліферативної фази та 54/39 = 1,38 для лютеїнової фази. Спостерігалось значне збільшення кількості випадків гострого апендициту серед менструальних жінок у лютеїновій фазі (p<0,05). Середній вік учасників дослідження становив 28,31 ± 9,56.

Висновки. *За результатами нашого дослідження можна зробити висновок, що захворюваність на гострий апендицит значно відрізняється різними фазами циклу менструації з найвищою частотою в лютеїновій фазі. Отже, жіночі гормони (естроген та прогестерон) відіграють важливу роль у виникненні гострого апендициту.*

КЛЮЧОВІ СЛОВА: гострий апендицит; фаза менструації; проліферативна фаза; лютеїнова фаза.

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References

1. Liang M, Andersson R, Jaffe B and Berger D. The Appendix | Schwartz's Principles of Surgery, 10th ed, New York; McGraw Hill Education Medical; 2015. 1241-62.

2. Arnbjörnsson E. Varying frequency of acute appendicitis in different phases of the menstrual cycle. Surg Gynecol Obstet. 1982 Nov;155(5):709–11.

3. Robinson JA, Burch BH. An assessment of the value of the menstrual history in differentiating acute appendicitis from pelvic inflammatory disease. Surg Gynecol Obstet. 1984 Aug;159(2):149–52.

4. Eldar S, Faraggi D, Abrahamson J, Schein M. The menstrual cycle and acute appendicitis. Eur J Surg. 1995 Dec;161(12): 897–900.

5. Souza SS, Castro FA, Mendonca HC, Palma PV, Morais FR, Ferriani RA, Voltarelli JC. Influence of menstrual cycle on NK activity. J. Reprod. Immunol. 2001;50:151–9.

6. Lee S, Kim J, Jang B, Hur S, Jung U, Kil K, Na B, Lee M, Choi Y, Fukui A, Gilman-Sachs A, Kwak-Kim JY. Fluctuation of peripheral blood T, B, and NK cells during a menstrual cycle of normal healthy women. J Immunol. 2010 Jul 1;185(1):756-62.

https://doi.org/10.4049/jimmunol.0904192.

7. Grimaldi CM, Cleary J, Dagtas AS, Moussai D, Diamond B. Estrogen alters thresholds for B cell apoptosis and activation. J Clin Invest. 2002 Jun; 109(12):1625-33.

https://doi.org/10.1172/JCI14873.

8. Mo R, Chen J, Grolleau-Julius A, Murphy HS, Richardson BC, Yung RL. Estrogen regulates CCR gene expression and function in T lymphocytes. J Immunol. 2005 May 15; 174(10):6023-9.

doi: 10.4049/jimmunol.174.10.6023.

9. Tanriverdi F, Silveira LF, MacColl GS, Bouloux PM. The hypothalamic-pituitary-gonadal axis: immune function and autoimmunity. J Endocrinol. 2003 Mar; 176(3):293-304.

https://doi.org/10.1677/joe.0.1760293.

10. Dosiou C, Hamilton AE, Pang Y, Overgaard MT, Tulac S, Dong J, Thomas P, Giudice LC. Expression of membrane progesterone receptors on human T lymphocytes and Jurkat cells and activation of G-proteins by progesterone. J Endocrinol. 2008 Jan; 196(1):67-77.

https://doi.org/10.1677/JOE-07-0317.

11. Hall OJ, Klein SL. Progesterone-based compounds affect immune responses and susceptibility to infections at diverse mucosal sites. Mucosal Immunol. 2017 Sep; 10(5):1097-1107.

https://doi.org/10.1038/mi.2017.35.

12. Speroff FA. Clinical Gynecologic Endocrinology and Infertility, 8th edn. Wolters Kluwers Lippincott Williams and Wilkins, Philadelphia, 2011.

13. Hardy DB, Janowski BA, Corey DR, Mendelson CR. Progesterone receptor plays a major anti-inflammatory role in human myometrial cells by antagonism of nuclear factor-κB activation of cyclo-

oxygenase 2 expression. Molecular endocrinology. 2006 Nov 1;20(11):2724-33.
https://doi.org/10.1210/me.2006-0112.
14. Jones LA, Kreem S, Shweash M, Paul A, Alexander J, Roberts CW. Differential modulation of TLR3- and TLR4-mediated dendritic cell maturation and function by progesterone. J Immunol. 2010 Oct 15; 185(8):4525-34.
https://doi.org/10.4049/jimmunol.0901155.
15. Lei K, Chen L, Georgiou EX, Sooranna SR, Khanjani S, Brosens JJ, Bennett PR, Johnson MR. Progesterone acts via the nuclear glucocorticoid receptor to suppress IL-1β-induced COX-2 expression in human term myometrial cells. PLoS One. 2012; 7(11):e50167.
https://doi.org/10.1371/journal.pone.0050167.
16. Grandi G, Mueller M, Bersinger N, Papadia A, Nirgianakis K, Cagnacci A, McKinnon B. Progestin suppressed inflammation and cell viability of tumor necrosis factor-α-stimulated endometriotic stromal cells. Am J Reprod Immunol. 2016 Oct; 76(4):292-8.
https://doi.org/10.1111/aji.12552.
17. Miyaura H, Iwata M. Direct and indirect inhibition of Th1 development by progesterone and glucocorticoids. J Immunol. 2002 Feb 1; 168(3):1087-94.
https://doi.org/10.4049/jimmunol.168.3.1087.
18. Ehring GR, Kerschbaum HH, Eder C, Neben AL, Fanger CM, Khoury RM, Negulescu PA, Cahalan MD. A nongenomic mechanism for progesterone-mediated immunosuppression: inhibition of K^+ channels, Ca^{2+} signaling, and gene expression in T lymphocytes. J Exp Med. 1998 Nov 2; 188(9):1593-602.
https://doi.org/10.1084/jem.188.9.1593.
19. Siiteri PK, Febres F, Clemens LE, Chang RJ, Gondos B, Stites D. Progesterone and maintenance of pregnancy: is progesterone nature's immunosuppressant? Ann N Y Acad Sci. 1977 Mar 11; 286:384-97.
https://doi.org/10.1111/j.1749-6632.1977.tb29431.x.
20. Whitacre CC, Reingold SC, O'Looney PA. A gender gap in autoimmunity. Science. 1999 Feb 26; 283(5406):1277-8.
https://doi.org/10.1126/science.283.5406.1277.
21. Cutolo M, Capellino S, Sulli A, Serioli B, Secchi ME, Villaggio B, Straub RH. Estrogens and autoimmune diseases. Ann N Y Acad Sci. 2006 Nov; 1089:538-47.
https://doi.org/10.1196/annals.1386.043.
22. Grimaldi CM, Jeganathan V, Diamond B. Hormonal regulation of B cell development: 17 beta-estradiol impairs negative selection of high-affinity DNA-reactive B cells at more than one developmental checkpoint. J Immunol. 2006 Mar 1; 176(5):2703-10.
https://doi.org/10.4049/jimmunol.176.5.2703.
23. Klein SL. Hormonal and immunological mechanisms mediating sex differences in parasite infection. Parasite Immunol. 2004 Jun-Jul; 26(6-7):247-64.
https://doi.org/10.1111/j.0141-9838.2004.00710.x.
24. Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. Neurosci Biobehav Rev. 2000 Aug; 24(6):627-38.
https://doi.org/10.1016/s0149-7634(00)00027-0.
25. Marriott I, Bost KL, Huet-Hudson YM. Sexual dimorphism in expression of receptors for bacterial lipopolysaccharides in murine macrophages: a possible mechanism for gender-based differences in endotoxic shock susceptibility. J Reprod Immunol. 2006 Aug; 71(1):12-27.
https://doi.org/10.1016/j.jri.2006.01.004.
26. Roberts BJ, Dragon JA, Moussawi M, Huber SA. Sex-specific signaling through Toll-Like Receptors 2 and 4 contributes to survival outcome of Coxsackievirus B3 infection in C57Bl/6 mice. Biol Sex Differ. 2012 Dec 15; 3(1):25.
https://doi.org/10.1186/2042-6410-3-25.
27. Young NA, Wu L, Burd CJ, Friedman AK, Kaffenberger BH, Rajaram MVS, et al. Estrogen modulation of endosome-associated toll-like receptor 8 : An IFN α -independent mechanism of sex-bias in systemic lupus erythematosus. Clin Immunol [Internet]. 2014; 151(1):66–77. Available from: http://dx.doi.org/10.1016/j.clim.2014.01.006 and https://www.sciencedirect.com/science/article/pii/S1521661614000114.

Received 19 May 2022; revised 27 May 2022; accepted 14 June 2022.