Differential Effect of Cyclooxygenases 1 and 2 in Late Reproductive Age Women

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Abstract:

Cyclooxygenases enzymes (COX) are related with ovulation, apoptosis and menstrual disorder. Several studies demonstrate that COX 1 is one of the major sources of prostaglandin but COX 2 is more important in the late reproductive age women. Prostaglandin is bioactive compound excreted from Arachidonic acid by Cox 1 and Cox 2, play role in the fertility and ovulation but when increased above the normal level especially in menstrual cycle, ectopic pregnancy is attributed to this cause. Cox 1 and Cox 2 inhibitors have been regulated the inflammatory responses include cytokines and tumor growth factors which produced from neutrophil cells by cyclooxygenases activation, it has been used to regular prostaglandin action, especially PGG2 and PGH2. Any changes in the endometrial cells lead to increased vascular inflammation that developed to the late reproductive disease. Steroidogenesis characterized by increased levels of estrogen in the uterus caused uterine infections and elevated cyclooxygenases levels especially during uterine contractions process.

Key words: Cyclooxygenases, Reproductive age women, Cytokines

التأثير التفاضلي لانزيمات الأكسجة الحلقية ١ و ٢ في تأخر سن الإنجاب لدى النساء

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الخلاصة:

ترتبط إنزيمات الأكسدة الحلقية مع الإباضة وموت الخلية المبرمج واضطراب الدورة الشهرية. تثبت العديد من الدراسات أن COX 1 هو أحد المصادر الرئيسية للبروستاجلاندين ، لكن COX 2 الأكثر أهمية في النساء المتأخرات في سن الإنجاب. البروستاكلاندين مركب حيوي يفرز من حامض الأراكيدونيك بواسطة COX 2 , COX 1 ويلعب دور في الخصوبة والإباضة ولكن عندما يزداد عن المستوى الطبيعي وخاصة في الدورة الشهرية يحدث الحمل خارج الرحم. تنظم مثبطات COX 2 , COX 1 الاستجابات الالتهابية والسيتوكينات وعوامل نمو الورم التي تنتج من الخلايا النيتروفيلية عن طريق تنشيط انزيمات الاكسدة الحلقية ، حيث تستخدم في تنظيم عمل البروستاكلاندين ، وخاصة PGG2 و PGH2. أي تغييرات في خلايا بطانة الرحم تؤدي إلى زيادة التهاب الأوعية الدموية والتي تتطور إلى مرض تاخر الانجاب. تسبب الستيرويد التي تتميز بارتفاع مستويات هرمون الاستروجين في الحالب مسببة التهابات الرحم وارتفاع مستويات انزيمات الأكسدة الحلقية خاصة أثناء عملية تقلص الرحم.

الكلمات المفتاحية: إنزيمات الأكسدة الحلقية ، النساء المتأخرات في سن الإنجاب ، سايتوكينز.

Introduction

Ovulation process depends on several causes, particularly hormonal factors such as pituitary gonadotropins, glucocorticoids hormone, follicular stimulating hormone, luteinizing hormone, and Prolactin besides environmental factors such as steroids, cytokine and other growth factors. Prostaglandin is one of the most important factors is related with reproduction and female genitalia. Cyclooxygenases levels effect on fertilization and ovulation. None steroidal anti-inflammatory is used in the treatment of the menstruation abundance and rheumatism. However, high administration of these drugs may delay the process of ovulation by decreased levels of Prostaglandin in the blood. Cox 1 was excreted in all tissues of the body and thus prolongs the action of Prostaglandin while the production of Cox 2 is stimulated in immune cells by cytokine excretions, mitogens and tumor necrosis factors [1]. Cox2 enzymes are directly responsible for the production of Prostaglandin during inflammation therefore used Cox2 inhibitors for treatment and decreased levels of inflammation. Recent studies are investigating the dangerous effects of increased intake of these drugs by women who are trying to conceive [1].

Late reproductive age can be caused by menstrual abnormalities, sudden bleeding of the uterus, endometriosis, uterine fibrosis, uterine thrombosis, ovulation failure and polycystic ovaries [2] Very few studies are diagnosed of late reproductive age women in earlier adulthood. Furthermore, the availability of eggs in ovary is an important factor in the fertilization and diagnosis of reproduction in the earlier stage, other studies recommended to determine ovaries size, vaginal ultrasound and measurement the number of vital hormones such as Anti-mullerian hormone (AMH). Women with late reproductive can be classified in three groups according to the type of treatment: conservative treatment, bilateral ovarian drilling and bilateral ovarian wedge resection as showed in the figure (1) [3]:

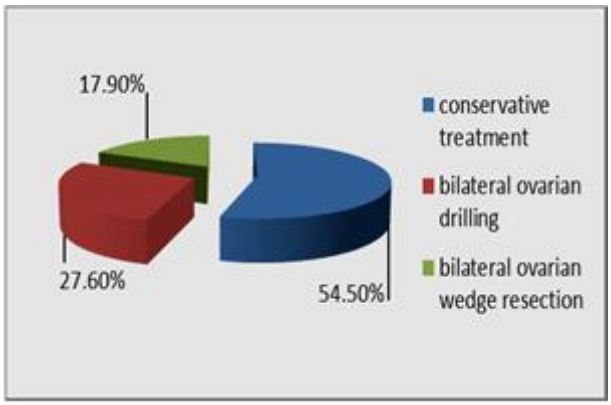

Figure (1): Women were divided by type of treatment

Cox 1 is maintenance of the mucosa of the stomach, kidney protection and thrombocytopenia while Cox 2 regulates the production of PGE2, inflammation and apoptosis. Arachidonic acid is converted to prostaglandins by action of cyclooxygenases 1 and 2 observed in fig 2. [(4)]. Endometriosis is a common disease in late reproductive age accompanied with pelvic pain considered as main causes of infertility due to defect in the immune system. Increased level of estrogen in the blood stimulate formation of macrophage in the uterine cavity and have the ability to protect uterus from infections and inflammation but if exceeds the normal could be caused of endometriosis. PGE2 and PGF2α increased in peritoneal fluid confirmed by many studies that demonstrate the relationship between

cyclooxygenases with PGE2 and PGF2α. Other researchers have been indicated the elevation of COX 1 in the peritoneal fluid of women with endometriosis as compared with healthy subjects [5].

NSAIDs and COX inhibitors are frequently used as treatment during pregnancy especially if increased inflammation and musculoskeletal weakness in the trimester stage while the complication of drugs was noticed in the eight months of pregnancy, it was attributable to increased pulmonary pressure [6]. Estrogen is involved to stimulate Cox 2 production during uterine contractions, which in turn increased prostaglandin production above the normal level, especially in menstrual cycle, so ectopic pregnancy is attributed to this cause. Many recent studies have shown that Cox 2 is influenced by metabolic changes associated with endometriosis in menstrual cycle [7].

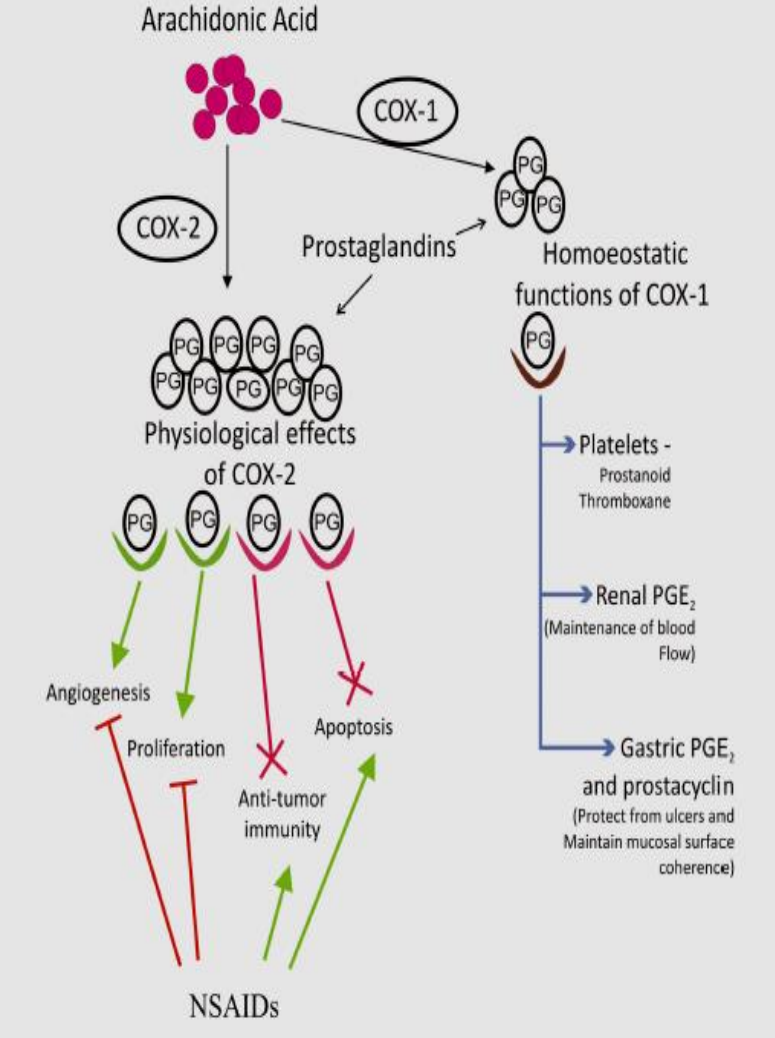

Figure (2): Arachidonic acid is converted to prostaglandins by action of cyclooxygenase 1 and 2 Cox-1 and Cox-2 enzymes (4)

Effect of Non-Steroidal anti-inflammatory drugs on cyclooxygenases in relation to ovulation

In the past years, statistical studies were appeared an increase in the number of late-reproductive age women have return to immunological causes [8]. Therefore, anti-inflammatory drugs are used to treat immune defect before and during pregnancy [9,10]. NSAIDs such as aspirin, ibuprofen and acetaminophen, which treat high fever and aches, have been known for

many years for their effects on enzymes particularly COX 1 and 2 because these enzymes were stimulating prostaglandin production from the Arachidonic acid [11]. COX 1 and 2 have the same function but work at different times and places. COX-1 coexist in diverse tissues such as the bone, membrane, brain and kidneys etc while COX-2 is difficult to diagnosed in many tissues, but it was present in gastrointestinal disorders such as intestinal inflammation and stimulate tumor growth factor- beta (TGF-β), which regulates many vital functions such as reproduction apoptosis and development of embryos[11].

Aspirin is a non-steroidal anti-inflammatory drug have inhibitors functions on the Cox 1 and 2 enzymes and regulates the action of prostaglandin especially PGG2 and PGH2. The group of anhydride aspirin acetylate protein of the enzyme by reacts with nucleophilic groups [12] and modified the serine residues active site of cyclooxygenases [13]. Acetylating of enzymes by aspirin expressed as anti-inflammatory and anti-platelet aggregation which play role of biochemistry and physiological functions.[14]

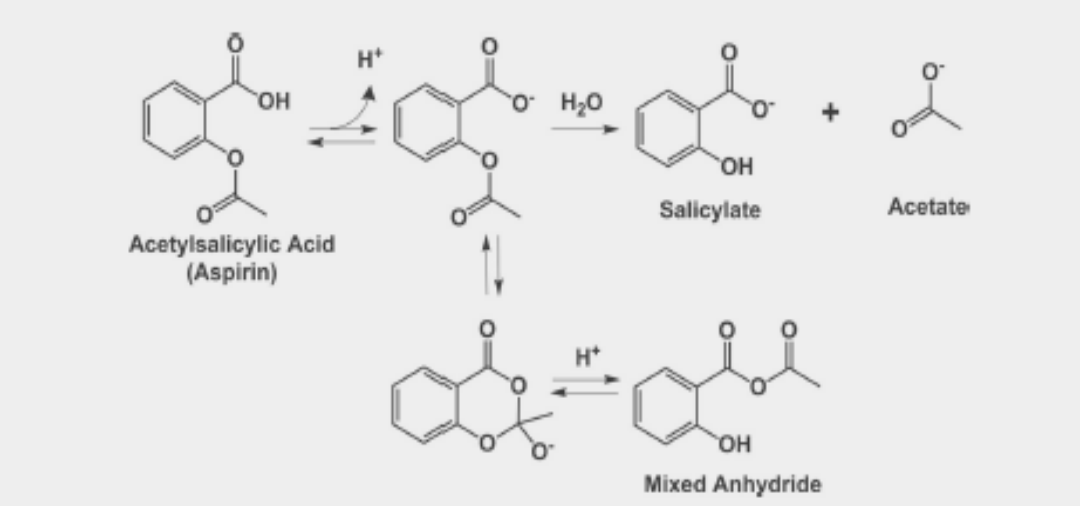

Figure (3): Acetylation of cyclooxygenases by aspirin (12)

In the past decades, researchers confirm that both azathioprine, cyclosporine and sulfasalazine have been used to treat inflammation in pregnancy, especially with increased of women's average age [10]. Ibuprofen or Naproxin particulary celecoxib, used significantly in the last trimester of pregnancy and proved to be effective in the inhibiting of COX 2 in late reproductive but increase the risk of preterm infants as a side effect [6]. These pharmacological effects decresed with age as a result of lower body water in older women and thus less protein binding [15].

Cyclooxygenases and Cytokines

Cytokine is specific immune proteins soluble participated in the reproductive system may complicate to abortion and preeclampsia which imbalance of Immune molecules can delay pregnancy. CD4+ T-helper cells have an active role in the immune balance process which divided into three types: Th1, Th2 Th0. Imbalances of these molecules related with increased levels of Prolactin in the blood beside elevated of progesterone level the main causes of late reproduction age women [16]. Recent studies were also reported that interferon plays an important role in promoting Prolactin and Luteinizing hormone [17].

Cytokines and growth factors induce secretion of the arachidonic acid from the cell membrane by cyclooxygenases. Inflammatory markers play role in pathogenesis diseases such as tumors and

immune system defection, it was produced in large quantities from macrophage in the acute inflammation depending on the immune system and secretion of Cox 1 and 2. Therefore Cyclooxygenases play important role for controlling excretion of cytokines from macrophage to the epithelial receptors in the tissue [18]
Endometrial immunity suppression is caused by acute infections, apoptosis and generation of vessels frequently while reduced levels of IFN, TNF-α, IL-12 and IL-1 was occurred by Cox2 inhibitors [19]. Transforming growth factor (TGF-β) is elevated in the peritoneal fluid in women with endometriosis; many studies were demonstrating the association between cyclooxygenases and TGF-β [20]. It was excreted from the endocrine glands of the endometrial fluid in three forms, TGFb2, TGFb1 and TGFb3. TGFb3 is expressed mainly in the uterus which confirmed by recent studies. TGFb2 and TGFb1 is present in almost cells [21] Tumor necrosis factor-alpha have multiple function excreted by monocyte which has an important effect in coagulation, insulin resistance, lipid metabolism and endothelial function while in high levels may lead to reproductive failure [22].

Conclusion

Increased level of estrogen in the blood stimulate formation of macrophage in the uterine cavity and have the ability to protect uterus from infections and inflammation but if exceeds the normal could be caused of endometriosis. Cyclooxygenases inhibitors have an important role in the ovulation and occurrence of reproduction by regulation of women sex hormones in the physiological responses however; high administration of inhibitors may delay the process of ovulation by decreased levels of Prostaglandin and cytokine in the blood.

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References

1- Peng-Hui W. Effect of a Selective Nonsteroidal Anti-inflammatory Drug, Celecoxib, on the Reproductive Function of Female Mice. J Chin Med Assoc. 2007:70(6):245-248.
2- Maśko M. Domino M. et al. Breeding management of mares in late reproductive age considering improvement of welfare. Journal of Animal and Feed Sciences. 2018:27(4): 285-291.
3- Ketevan B. Ludmila B. Ovarian reserve in women of late reproductive age by the method of treatment of PCOS: Iran J Reprod Med. 2015:13 (5): 263-268.
4- Jaya G. Lohit K. et al. Role of Modulator of Inflammation Cyclooxygenase-2 in Gammaherpesvirus Mediated Tumorigenesis.2017:28(8):538
5- Meng H. et al. Distinct mechanisms regulate cyclooxygenase-1 and -2 in peritoneal macrophages of women with and without endometriosis Molecular Human Reproduction. 2002: 8(12): 1103-1110.
6- Anick B. et al. Risk of preterm birth following late pregnancy exposure to NSAIDs or COX-2 inhibitors. 2018: 159(5): 948-955
7- Esin K. Serap K. Esra B. · Mine Genc N.· Serkan G.Investigation of the Roles of Cyclooxygenase-2 and Galectin-3 Expression in the Pathogenesis of Premenopausal Endometrial Polyps . Journal of Pathology and Translational Medicine .2016: 50(3): 225-230.
8- Mathews T. Hamilton B. Mean age of mothers is on the rise: United States, 2000–2014. NCHS Data Brief. 2016:1(232):1-8.
9- Andreoli L. Bertsias G. Agmon-Levin N. Brown S. Cervera R. et al. recommendations for women's health

and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 2017:76(3):476–85.
10- Gotestam C. Hoeltzenbein M. Tincani A. Fischer-Betz R. Elefant E. Chambers C. da Silva J. Nelson-Piercy C. et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016: 75(5):795-810.
11- Buket B. et al. Immunohistochemical Distribituon of COX-1, COX-2, and TGFβ-1 in the Duodenum of Rats Treated with Capsaicin. Kafkas Univ Vet Fak Derg. 2016:22 (3): 333-338.
12- Argentina O. et al. Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention; Cancer Metastasis Rev. (2017): 36:289–303.
13- Lucido, M. Orlando, B. Vecchio, A. &Malkowski, M. Crystal structure of aspirin-acetylated human cyclooxygenase- 2: insight into the formation of products with reversed stereochemistry. Biochemistry.2016:55(8): 1226–1238.
14- Schafer, A. Bauersachs, J. Endothelial dysfunction, impaired endogenous platelet inhibition and platelet activation in diabetes and atherosclerosis. Current Vascular Pharmacology. 2008: 6(1): 52–60.
15- Supakanya W. Amaraporn W. et al. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. 2018: 9(1): 143-150.
16- Noura A. et al. Identification of serum cytokines as markers in women with recurrent pregnancy loss or miscarriage using MILLIPLEX analysis. Biomedical Research 2018: 29 (18): 3512-3517.
17- Kaur R, Gupta K. Endocrine dysfunction and recurrent spontaneous abortion: an overview. Int J Appl Basic Med Res. 2016: 6(2): 79-83.
18- Natalia Ł. et al. Expression and Activity of COX-1 and COX-2 in Acanthamoeba sp.-Infected Lungs According to the Host Immunological Status. Int. J. Mol. Sci. 2018: 19(1):121.
19- Samoshkin1 N. Yarmolinskaya M. Polyakova V. The Efficacy of Selective Cyclooxygenase 2 Inhibitors In The Treatment Of Genital Endometriosis. Journal of Obstetrics and Women's Diseases. 2018: 67(2):52-60.
20- Sutrisno S. et al. The effect of genistein on TGF-b signal, dysregulation of apoptosis, cyclooxygenase-2 pathway, and NF-kB pathway in mice peritoneum of endometriosis model. Middle East Fertil Soc J .2017:22(4): 295-299.
21- Rebecca L. TGF-b superfamily expression and actions in the endometrium and placenta. Reproduction. 2006:132(2): 217–232.
22- El-Far M. El-Sayed IH. El-Motwally AE. Hashem IA. Bakry N. Serum levels of TNF-alpha and antioxidant enzymes and placental TNF-alpha expression in unexplained recurrent spontaneous miscarriage. J Physiol Biochem 2009: 65(2): 175-181.