Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/17514
DOI URL: http://dx.doi.org/10.21474/IJAR01/17514

RESEARCH ARTICLE

THE ROLE OF LUTEINIZING HORMONE (LH) RECEPTOR IN THE REGULATION OF OOCYTE MATURATION: A SYSTEMATIC LITERATURE REVIEW

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Manuscript Info

Manuscript History
Received: 10 July 2023
Final Accepted: 14 August 2023
Published: September 2023

Key words:-
LH Receptor, Human Oocyte Maturation, Ovarian Cycle

Abstract

The hormone luteinizing hormone (LH) is an important glycoprotein hormone that controls the activity of the gonadal organs, which in turn affects the physiology of the menstrual cycle. For LH to exert its effects, its specific receptor (LHR) must be expressed by cumulus cells.
Objective: To determine the role of LH receptors (Luteinizing Hormone) in the regulation of human oocyte maturation processes
Method: Systematic Literature Review (SLR). Data collection was conducted by documenting all articles based on predefined inclusion and exclusion criteria. A total of 10 national and international journal articles were retrieved from databases such as Google Scholar, PubMed, and Science Direct, using specific keywords related to the role of LH receptors and oocyte maturation. The literature search and study selection process followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.
Results: The highest expression of Luteinizing Hormone Receptor (LHR) observed in preovulatory follicles. Cumulus cell maturation, covering 100% of the oocytes, was 74%. FSHR and LHR mRNA expression levels increased with an increase in LH concentration in the in vitro maturation (IVM) medium. After 24 hours of IVM, there was a significant downregulation in the expression of LHR and FSHR.The mRNA and protein levels of FSHR and LHR in the cumulus-oocyte complex gradually decreased with increasing doses of FRBI in the IVM media compared to the control group. Majority of the cumulus cells from MII oocytes had RGS2/B2M gene expression of more than 50%. LH receptor expression in granulosa cells positively correlated with morphology, oocyte maturity, and fertility rate in the poor responder group. Granulosa cells from an agonist-triggered cycle with recombinant human chorionic gonadotropin (rhCG) for 24 hours were observed to increase viability, regulate mRNA expression of 3β-HSD, LH receptor, VEGF, and BCL-L2. More than 50% of the oocytes are matured after hCG injectionat an hCG concentration of 119.8 mIU/mL.
Conclusion:LH needs receptor binding and expression for proper function, resulting in improved oocyte maturation with optimal LHR concentration which is 10 µg/mL LH. LHR expression is highest in preovulatory follicles. LHR expression increases during antral follicle growth. Supplementing media with hCG improves oocyte maturity with a 77 mIU/mL cutoff value. Supplementation with FRBI reduce

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LHR expression in COCs. The number of cumulus cells can also indicate the level of oocyte maturity, where cumulus cells covering 100% of the oocytes show the highest oocyte maturation.

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Introduction:-

The hormone luteinizing hormone (LH) is an important glycoprotein hormone that controls the activity of the gonadal organs, which in turn affects the physiology of the menstrual cycle. Theca, granulosa, and cumulus cells expressing LH receptors (LH-R) are how LH functions (Wiweko, Satria, et al., 2019). LH binds to LH-R, which is a part of the cell membrane and belongs to the G-protein-coupled receptor family. It has seven transmembrane domains and a large N-terminal extracellular domain. For LH to exert its effects, its specific receptor (LHR) must be expressed by cumulus cells (Wei et al., 2017).

The use of gonadotropins is crucial for ovarian stimulation. Its introduction into medical practice almost a century ago marked a significant development in infertility treatment. While LH is important in promoting steroidogenesis and the development of primary follicles, FSH is the main regulator of antral follicle growth. Additionally, LH carries out various tasks at different times during natural and stimulated cycles (Alviggi et al., 2018).

In humans, the early events of follicular maturation primarily consist of granulosa cell mitosis and stromal transformation into a theca cell layer, stimulated by increasing levels of FSH and LH. In rodents and humans, luteinizing hormone regulates androgen biosynthesis by the theca-interstitial cells during follicle development, and these androgens are converted to estrogen by the granulosa cells. The main drivers of the ovarian cycle are the sequential and combined actions of FSH and LH. While the action of FSH is limited to granulosa cells within the ovarian follicle, LH acts on multiple targets including the theca-interstitial cells, FSH-stimulated granulosa cells, and the corpus luteum after ovulation (Menon et al., 2018).

In a study by Wiweko et al. (2019), the morphology, oocyte maturity, and fertility rate showed a positive correlation with granulosa LH-R expression in the poor ovarian response group and a negative correlation in the good ovarian response group. This indicates that although high LH-R expression in granulosa cells is observed in the good ovarian response group, it does not affect oocyte maturation, morphology, or fertility rate. However, in the poor ovarian response group, LH is necessary for oocyte growth and maturation (Wiweko, Luky Satria, et al., 2019).

"The quality of oocytes can be predicted by mRNA expression of LHR in cumulus cells. Yang et al. studied 35 women with Polycystic Ovary Syndrome (PCOS) undergoing 50 cycles of In Vitro Maturation (IVM) to examine the mRNA expression of LHR in cumulus cells. Oocytes were retrieved 36 hours after patients received 10,000 IU of HCG, administered on cycle days 7 and 13. The study found that the blastocyst rates derived from oocytes with scattered cumulus cells were significantly higher compared to oocytes with compact and sparse cumulus cells, despite the small number of embryos examined. Therefore, the results of this study indicate that the presence of scattered cumulus cells at the time of oocyte retrieval may positively correlate with oocyte maturation and blastocyst development in the primary Human Chorionic Gonadotrophin (HCG) IVM cycle. Additionally, the results also suggest that the expression of LH-R in cumulus cells may correlate with the cumulus cell pattern at that time (Yang et al., 2005).

In a study conducted by Amansyah (2016), using immature bovine oocytes divided into three groups based on the cumulus cell pattern on germinal vesicle-stage oocytes of 2-8 mm with three layers of cumulus cells. Cumulus cells in Group A covered the entire oocyte, cumulus cells in Group B covered more than 50% of the oocyte, and cumulus cells in Group C only partially covered the oocyte. All three groups underwent IVM using Tissue Culture Medium (TCM) supplemented with Human Menopausal Gonadotrophin (HMG) at 0.1 IU/ml along with 10% Follicle Fluid. The maturity of cumulus cells covering all oocytes was higher compared to cumulus cell morphologies covering the majority and a small portion of the oocytes, with ratios of 74%, 60%, and 12% respectively(Amansyah, 2016).

The maturation of oocyte meiosis is a crucial step in oocyte development. During this process, a surge of LH releases the oocyte from prophase meiosis arrest and induces the resumption of oocyte meiosis and completion of the first meiotic division. The Cyclic Adenosine Monophosphate (cAMP) system is activated when LH binds to LH receptors on mural granulosa cells, leading to the activation of G proteins. It can be understood that the proteins

controlling oocyte meiosis maturation are targeted by LH signals in the follicle and oocyte compartments. The C-Type Natriuretic Peptide/Natriuretic Peptide Receptor 2 (CNP/NPR2) system, Epidermal Growth Factor (EGF) signaling, and gap junctions are the main LH signaling targets in the ovarian follicle compartment. Maturation factors are the primary targets of LH signaling in the oocyte (Arroyo et al., 2020).

There has been limited research on human oocyte maturation due to the scarcity of available human oocytes for research purposes. It is only recently that human oocytes have been studied extensively. Most human oocyte research has been conducted in the past 40 years, thanks to the availability of human oocytes through advancements in human IVF. IVF clinics provide oocytes for research in most human oocyte studies(Arroyo et al., 2020).

Given the current abundance of recent research developments and the lack of comprehensive reviews on the role of LH receptors in regulating human oocyte maturation, this review aims to uncover the role of LH receptors (Luteinizing Hormone) in the regulation of oocyte maturation. Furthermore, this review is expected to serve as valuable input in determining the success of oocyte maturation in natural and stimulated cycles

Methods:-

The design of this study was a Systematic Literature Review (SLR). SLR is a term used to refer to a specific research methodology and development that is conducted to gather and evaluate relevant research on a specific topic of focus (Triandini et al., 2019). The research methodology employed in this study was descriptive analysis, which involved the systematic breakdown of collected data before providing understanding and justification for readers to fully comprehend it. The objective of this method was to review several journals to determine the role of LH receptors in oocyte maturation.

National and international journals were used as the research population and were determined based on inclusion and exclusion criteria. The search for published articles was conducted through Google Scholar, PubMed, and Science Direct using selected keywords, namely LH Receptor and oocyte maturation. Literature search using keywords and the addition of the notation "and" were used to specify the search for research articles. The database search used keywords enclosed in quotation marks (" ") to make the results more specific and was further specified by setting the range of publication years.

Literature search and study selection were conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) strategy. From the filtration based on abstract reviews, a total of 26 journals were identified, which were further filtered based on full text. Out of the initial total of 26 journals, 10 journals were obtained in the full text review stage, while the rest were excluded for not meeting the inclusion criteria. The filtered journals that met the inclusion criteria were then subjected to another filtration to assess their quality. Journals that passed the quality assessment were subsequently analyzed.

This Systematic Literature Review is synthesized using a narrative method by grouping similar data extracted results according to the measured outcomes to answer the objectives. Research journals that meet the inclusion criteria are then collected, and journal summaries are created, including the researchers' names, publication year, research title, methods, and summary of findings. These journal summaries are entered into a table following the aforementioned format. To further clarify the analysis, the abstracts and full texts of the journals are read and scrutinized. The journal summaries are then analyzed regarding the content contained in the research objectives and the research findings. Content analysis of the journals is performed by coding the reviewed journal content based on the overall outline or core of the research, which is done by paraphrasing into a sentence. Once collected, similarities and differences among each study are identified and discussed to draw conclusions.

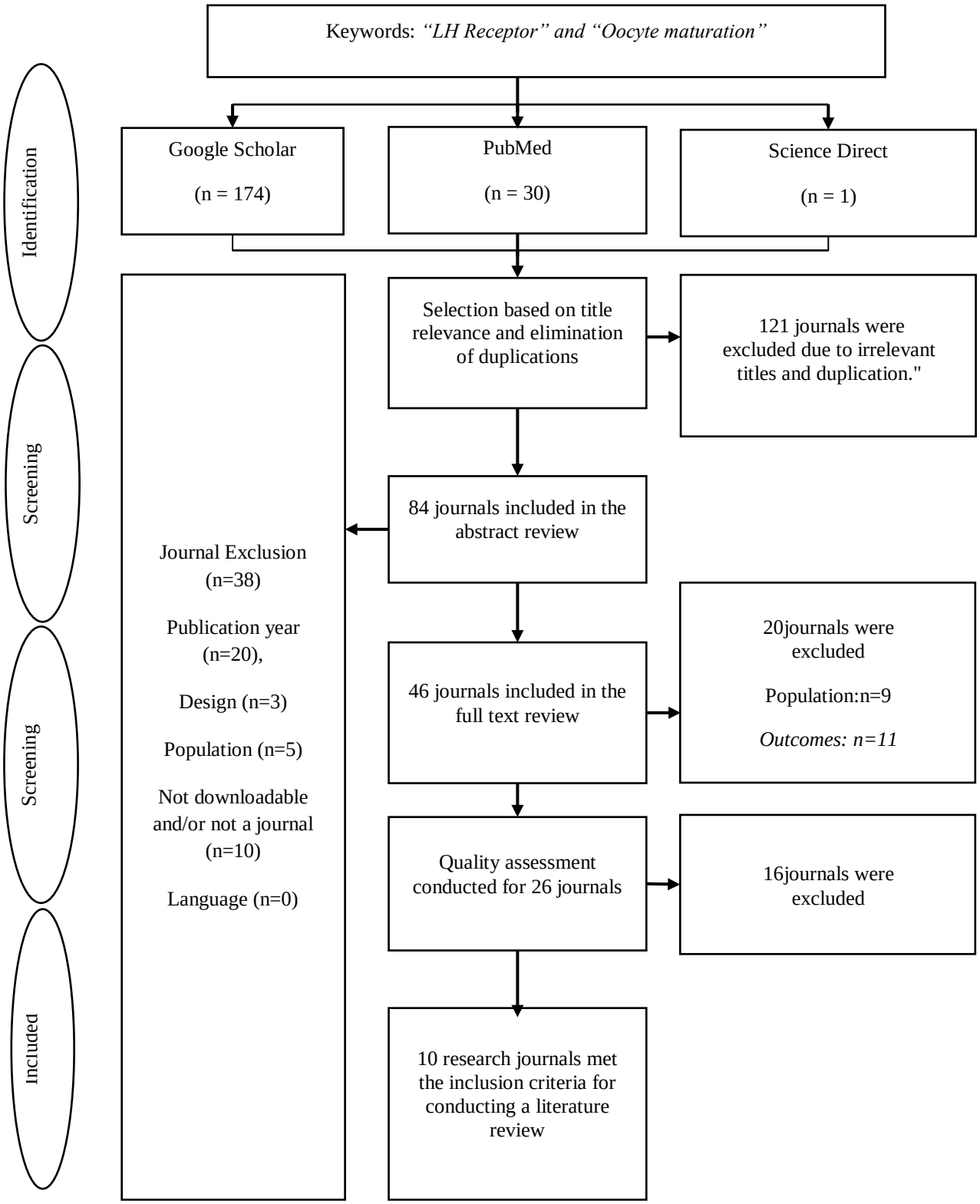

Figure 1:- PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Strategy for Journal Selection.

Results:-

Table 1:- Synthesis of Data Results.

Authors and Name	Title	Research Design	Research Subject	Results

(Maman et al., 2012)	High Expression Of Luteinizing Hormone Receptors Messenger RNA By Human Cumulus Granulosa Cells Is In Correlation With Decreased Fertilization	Cross-Sectional Study	The study involved 70 patients undergoing in vitro fertilization (IVF) and 20 patients undergoing in vitro maturation (IVM).	The expression of LHR increases during antral follicle growth, with the highest expression observed in preovulatory follicles, and there is a correlation between LHR expression and pregnancy rate. Lower expression levels of LHR in cumulus granulosa cells correlate with lower oocyte maturity, while excessive expression correlates with lower fertilization rates.
(Amansyah, 2016)	The Number of LH Receptor could Predict the Success of Oocyte Maturity in the Process of In Vitro Maturation	Experimental Study	300 oocytes derived from cows.	The study showed that the average number of LH receptors in the three groups (A, B, C) were 183.4, 78.8, and 24.0, respectively. The research findings indicated that the larger the number of cumulus cell-oocyte complexes, the greater the influence on oocyte maturation. In group A, the maturity of cumulus cells fully covering the oocyte was 74%. In group B, the maturity of cumulus cells covering > 50% of the oocyte was 60%. In group C, the maturity of cumulus cells covering < 50% of the oocyte was 12%.
(Wei et al., 2017)	Evaluation of luteinizing hormone regulation of maturation and apoptosis, expression of LHR and FSHR in cumulus-oocyte complexes in Lanzhou fat-tailed sheep	Experimental Study	The ovaries were collected from 530 prepubertal and non-cyclic Lanzhou sheep, aged 6-7 months.	The mRNA expression levels of FSHR and LHR increase with the increase in LH concentration in the IVM media. The highest mRNA expression levels of FSHR and LHR were found in the LH-5 and LH-3 groups. However, there were no significant differences in FSHR protein expression among all the groups. On the other hand, the protein expression of LHR increased. The protein level of LHR in the LH-2 group was higher compared to the LH-1 group. These findings indicate that LH supplementation can enhance LHR protein expression.
(Dhali et al., 2017)	Temporal expression of cumulus cell marker genes during in vitro maturation and oocyte developmental competence	Experimental Study	sheep ovary	• At the early stage of IVM (0 hours), the expression of cumulus PTGS2, STAR, syndecan 2 (SDC2), LH receptor (LHR), fibroblast growth factor 2 (FGF2), BCL2, IL7RA, HSPA1A, and IFNT was significantly regulated in BCB- CC compared to BCB+ oocytes. • At the mid-stage of IVM (12 hours), the expression of

				cumulus STAR and FGF2 was significantly regulated, and the expression of IFNT was significantly downregulated by less than 0.30-fold in BCB- CC compared to BCB+ oocytes. • At the completion of IVM (24 hours), there was a significant downregulation in the expression of GREM1, HAS2, STAR, SDC2, LHR, FSHR, FGF2, BCL2, and IFNT. There was a significant upregulation in the expression of IL7RA by 1.92-fold in BCB- CC compared to BCB+ oocytes. • The significant downregulation in the expression of LHR and FSHR in poor-quality oocyte CC at the completion of IVM was demonstrated in this study. The results indicate that the cumulus expression of both genes is crucial for oocytes to acquire developmental competence at the final maturation stage.
(Suocheng & Liang, 2017)	FSHR and LHR Expression and Signaling as Well as Maturation and Apoptosis of Cumulus-Oocyte Complexes Following Treatment with FSH Receptor Binding Inhibitor in Sheep	Experimental Study	The ovaries were obtained from 509 prepubertal and noncyclic female sheep (aged 6-7 months).	The mRNA and protein levels of FSHR and LHR in the cumulus-oocyte complex gradually decrease with the addition of FRBI dose to the IVM media compared to the control group (CG), with the lowest values observed in the FRBI-4 group. FRBI treatment can reduce the expression of FSHR and LHR mRNA and protein in a dose-dependent manner in the sheep cumulus-oocyte complex. FRBI treatment can suppress the protein and mRNA expression of FSHR and LHR in the sheep cumulus-oocyte complex.
(Chokjirawat et al., 2018)	Luteinizing Hormone Receptor Gene and Regulator of G-protein Signaling 2 Gene Expression Level and Association with Oocyte Maturity in In vitro Fertilization/Intracytoplasmic Sperm Injection Cycle	Cross-Sectional Study	Cumulus granulosa cells (CCs) were collected from 59 oocytes obtained from 18 women undergoing IVF/ICSI treatment.	The expression levels of RGS2/B2M and LHR/B2M genes in CCs from human oocytes were assessed using controlled ovarian stimulation with an antagonist GnRH protocol using ddPCR technique. The majority of CCs from MII oocytes exhibited more than 50% expression of RGS2/B2M gene and showed significant differences. There was no difference in the expression of LHR/B2M gene between the

				immature and mature oocyte groups. As mentioned above, a relationship was observed between LH receptor and RGS2 protein. The antagonist GnRH protocol program indicated that maturity is not primarily dependent on LH receptor function; on the other hand, it is also dependent on RGS2 gene function.
(Wiweko, Luky Satria, et al., 2019)	Correlation between luteinizing hormone receptor gene expression in human granulosa cells with oocyte quality in poor responder patients undergoing in vitro fertilization: A cross-sectional study	Cross-Sectional Study	Women undergoing IVF procedures based on the Bologna criteria.	The expression of Granulosa LH-R is higher in poor ovarian responders compared to good ovarian responders, although not statistically significant. Granulosa LH-R expression correlates positively with oocyte morphology, maturity, and fertility rate in the poor responder group and negatively correlates in the good responder group.
(Bildik et al., 2019)	Luteal granulosa cells from natural cycles are more capable of maintaining their viability, steroidogenic activity and LH receptor expression than those of stimulated IVF cycles	Comparative translational research study	A total of 154 IVF patients were included in the study over a period of 6 months.	The decreased viability and damaged mRNA expression levels of LH receptor and anti-apoptosis gene BCL-L2 in cells from antagonist-triggered cycles, along with the additional damaged mRNA expression of 3β-HSD and VEGF in agonist-triggered antagonists, may explain the compromised luteal function in stimulated IVF cycles. GCs from agonist-triggered cycles incubated with rhCG for 24 hours were observed to increase viability, regulate mRNA expression of 3β-HSD, LH receptor, VEGF, and BCL-L2, and enhance P4 output from the cells compared to GCs not incubated with hCG.
(Owens et al., 2019)	Gene Expression in Granulosa CellsFrom Small Antral Follicles From Women With or Without Polycystic Ovaries	Experimental Study	GCs (granulosa cells) were obtained from 31 women (98 follicles), including 10 with polycystic ovary syndrome (PCOS) and 21 without PCOS. GLCs were	The expression of LH receptor did not correlate with follicle size within the range of hSAF used in this study. There was no overall increase in LHCGR expression in PCOS; however, a subpopulation of PCOS follicles (20%) showed up to a 20-fold higher expression of LHCGR compared to the average expression in GCs from normal ovaries. LHCGR functions only after antral follicles reach a diameter of approximately 8 to 10 mm (and only in dominant follicles) during the latter half of the follicular phase of a normal cycle.

			collected from 6 women with PCOS and 6 control subjects undergoing IVF.	
(Chananya et al., 2020)	Impact of Serum Human Chorionic Gonadotropin and Luteinizing Hormone Receptor Expression to Oocyte Maturation Rate: A Study of Controlled Ovarian Stimulation	Cross-Sectional Study	Thirty women undergoing Assisted Reproductive Technology (ART) cycles who met the inclusion criteria were included in the study.	More than 50% of oocytes were matured after hCG injection. When patients were grouped based on the percentage of matured oocytes, higher oocyte maturation correlated with higher serum hCG levels at 12 hours post-injection. At a serum hCG titer of 119.8 mIU/mL, all oocytes were matured, whereas at 60.5 mIU/mL, the maturation rate was less than 50%. The LHR level was approximately the same among the three graded groups (~5.1 AU), while the maturation rates for Group I, II, and III were 100%, 70%-99%, and 50%-69%, respectively. In Group IV, the LHR level was only 3.5 AU, indicating a maturation rate of less than 50%. The serum hCG cutoff value for predicting a high maturation rate was 77 mIU/mL.

The highest expression of LHR is found in preovulatory follicles, and there is a relationship between LHR expression and increased oocyte maturity. LHR expression increases during the growth of antral follicles. While excessive expression is associated with higher fertilization rates, lower LHR expression in cumulus GC is associated with lower oocyte maturity (Maman et al., 2012). Although not statistically significant, granulosa LH-R expression is higher in poor ovarian responders compared to good responders. In the poor responder group, granulosa LH-R expression correlates positively with oocyte morphology, maturity, and fertility rates, whereas in the good responder group, it correlates negatively (Wiweko, Satria, et al., 2019).

LHCGR expression is higher in granulosa lutein cells (GLCs) compared to granulosa cells (GC), especially in women with PCOS. LHCGR functions only after antral follicles reach a diameter of approximately 8 to 10 mm (and in dominant follicles) during the second half of the follicular phase of a normal cycle (Owens et al., 2019).

A study conducted on three groups differentiated based on the number of cumulus cells covering the oocyte showed that the increasing number of cumulus cells influences oocyte maturity. In the group with 100% cumulus cell coverage, the oocyte maturity rate was 74%. In the group with >50% cumulus cell coverage, the maturity rate was 60%. In the group with <50% cumulus cell coverage, the maturity rate was 12% (Amansyah, 2016).

LHR expression increases when LH concentration increases. An experiment conducted on five groups of oocytes (LH-1, LH-2, LH-3, LH-4, LH-5) with the addition of LH at different doses (0, 5, 10, 20, 30) found that adding 10 µg/mL LH (Luteinizing Hormone) in the LH-3 group was the optimal concentration with a maturation ratio of 44.3%. Adding LH doses <10 µg/mL or >10 µg/mL showed lower maturation ratios. This indicates that the addition of LH can increase LHR expression when given at an optimal dose (Wei et al., 2017).

LHR expression in developing oocytes can be observed using Brilliant cresyl blue (BCB) staining. Oocytes with different developmental capacities can be separated from the heterogeneous group using non-invasive BCB

technique. Oocytes absorb BCB staining after incubation in the staining solution, where it is then metabolized by the intracellular enzyme glucose-6-phosphate dehydrogenase (G6PDH). If compared to growing oocytes, the concentration of G6PDH is higher. As a result, after incubation, rapidly growing oocytes metabolize the stain and become colorless (BCB-), while slowly growing oocytes with lower G6PDH activity remain blue-stained (BCB+) (Dhali et al., 2017).

The expression of LHR was significantly found in growing oocytes (BCB-). During mid-oocyte maturation, LHR expression was not significantly detected. However, there was a significant downregulation of LHR expression during late oocyte maturation. The significant downregulation in LHR expression suggests that in the final stages of maturation, the cumulus expression of LHR is crucial for the oocyte to acquire developmental competence (Dhali et al., 2017).

The mRNA and protein levels of FSHR and LHR in the Cumulus-oocyte complexes gradually decreased with the addition of FRBI doses in IVM media compared to the control group (CG). FRBI treatment dose-dependently reduced the expression of FSHR and LHR mRNA and protein in sheep Cumulus-oocyte complexes. These findings indicate that FRBI treatment can decrease the levels of FSHR and LHR mRNA and protein expression in sheep COCs. FRBI suppresses the mRNA and protein expression of FSHR and LHR in sheep Cumulus-oocyte complexes (Suocheng & Liang, 2017).

The expression levels of the RGS2/B2M and LHR/B2M genes in human oocyte CCs using controlled ovarian stimulation with GnRH antagonist protocols were detected using ddPCR technique. An association was observed between LH receptor and RGS2 protein. The GnRH antagonist protocol program showed that oocyte maturation primarily depends not only on LH receptor function but also on RGS2 gene function (Chokjirawat et al., 2018).

GCs from cycles triggered by agonist rhCG for 24 hours were observed to significantly increase viability, regulate mRNA expression of 3β-HSD, LH receptor, VEGF, and BCL-2, and enhance P4 output from cells compared to their counterparts not incubated with hCG. When patients were grouped based on the percentage of mature oocytes, higher oocyte maturation correlated with higher serum hCG levels at 12 hours post-injection. At a hCG titer of 119.8 mIU/mL, all oocytes were mature, while at 60.5 mIU/mL, the maturation rate was <50%. The predictive threshold value of serum hCG for high maturation rate was 77 mIU/mL(Bildik et al., 2019; Chananya et al., 2020).

Discussion:-

The luteinizing hormone (LH) hormone controls the activity of the gonad organ, which in turn affects the physiology of the menstrual cycle. LH binds to LH-R, a part of the cell membrane that belongs to the G-protein-coupled receptor family and has seven transmembrane domains and a large N-terminal extracellular domain. In order for LH to function, its specific receptor (LHR) must be expressed. Theca cells, granulosa cells, and cumulus cells are known to express the LH receptor (LHR). It has been found that the number of cumulus cells can indicate the level of oocyte maturation. Oocytes completely covered by cumulus cells indicate the highest oocyte maturation. It can be concluded that a greater number of cumulus cells indicates higher LHR expression. (Amansyah, 2016).

The expression of LHR is associated with LH concentration. The optimal LH concentration that provides the highest maturation ratio is 10 µg/mL, while concentrations below or above 10 µg/mL indicate the opposite effect (Wei et al., 2017). This is consistent with the study by Deswal et al. (2019), where an increase in LH levels stimulates the theca cells in the ovary to produce more androgen. However, this is debated because excessive LH concentration can lead to PCOS, where an important biochemical characteristic of PCOS is high circulating LH levels, resulting in a low oocyte maturation ratio in PCOS patients(Deswal et al., 2019).

In the study by Wiweko et al. (2019), the group with poor ovarian response requires LH for oocyte growth and maturation, while in the group with good ovarian response, high granulosa LH-R expression affects oocyte maturity, morphology, and fertility rate. This study is consistent with the research conducted by Owens et al. (2019), where granulosa LH-R expression was higher in poor responders compared to good responders, although not statistically significant. In the group of poor responders, granulosa LH-R expression positively correlated with oocyte morphology, maturity, and fertility rate, while in the group of good responders, it showed a negative correlation. (Owens et al., 2019)

A study by Maman et al. (2012) explains that LHR mRNA is expressed at higher levels in granulosa cells of mature oocytes compared to immature oocytes, metaphase 1, and germinal vesicle oocytes. However, higher expression of LHR mRNA was associated with a decrease in fertilization rates. However, this current study provides contrasting results where the highest expression of LHR is found in oocytes undergoing maturation, specifically in preovulatory follicles.(Maman et al., 2012)

This can be attributed to the functional requirement of LH receptors in maintaining reproductive function, such as follicular growth and ovarian luteal cell function. LH receptors are necessary for the ovulation process in women and for the early maintenance of pregnancy by sustaining progesterone levels. In women, LH receptors are expressed in interstitial cells, granulosa cells, and theca cells for the development of follicles that produce and synthesize estrogen from androgen precursors. In luteal cells, LH receptors support ovulation, corpus luteum formation, and progesterone secretion. In granulosa and theca cells, LH receptors stimulate follicular maturation and steroidogenesis(Amansyah et al., 2017).

The expression of LHR also increases during the growth of antral follicles, especially at the 8-10 mm antral diameter. This applies only to dominant follicles from normal cycles. The same was also demonstrated in a previous study by Jeppesen et al. (2012). The study showed that LHR gene expression peaked in preovulatory follicles of granulosa cells just before induced ovulation, but LHR expression was also observed in the majority of follicles with a diameter of about 5 mm, although at approximately 10 times lower levels. Although LHR expression is present in mature follicles as well, it is about five times lower than before ovulation induction. Collectively, these previous studies indicate that LHR expression is not limited to large preovulatory follicles but is also expressed in granulosa cells of small antral follicles. (Jeppesen et al., 2012)

The addition of certain supplements can also affect the expression of LH receptors (LHR). In this study, it was found that supplementation with hCG can increase the percentage of mature oocytes at 12 hours post-injection. This is consistent with a study by Nora et al. (2020) where immature oocytes were matured in culture media with the addition of hCG. Despite the lack of significant differences, hCG still showed the best results in initiating meiosis resumption. When hCG supplementation was added, the rate of GV (Germinal vesicle) to MII evolution was higher compared to the control group. Additionally, hCG supplementation accelerated the MI to MII evolution. In this study, the predictive threshold value of hCG for a high level of maturation was found to be 77 mIU/mL.(Nora et al., 2020)

For clinical applications, most oocytes are obtained from ovarian follicles of women who have been administered hormones to induce the growth of more follicles. The use of hormones has resulted in follicles at different stages. Generally, oocytes are retrieved before the LH surge, and the oocytes are in the GV stage (Germinal vesicle). Studies using animal oocytes have shown that the endocrine environment plays a crucial role in ensuring normal cytoplasmic maturation and fertilization. The addition of HMG (human menopausal gonadotrophin) in the IVM (in vitro maturation) culture media can enhance the rate of maturation and fertilization (Amansyah et al., 2017).

Supplementation with FRBI can reduce the expression of LHR in COCs (cumulus-oocyte complexes). The level of apoptosis and the maturation rate of sheep COCs can be altered with FRBI supplementation depending on the dosage. The production of IP3, a second messenger involved in signal transduction pathways in various types of cells, is slightly promoted at lower doses of FRBI treatment but inhibited at higher doses. The expression of mRNA FSHR and LHR in COCs from sheep is suppressed by FRBI at both the mRNA and protein levels. As a result, FRBI prevents the synthesis of caspase-3 and FSH.

Apoptosis is regulated by the activation of several genes encoding proteins called caspases. Caspases are a part of cysteine proteases that become active during cell development and serve as active signals for cell destruction. The addition of FRBI is believed to inhibit the regulation and activation of factors that trigger apoptosis. GVBD (Germinal Vesicle Breakdown) is likely to occur through an indirect action mediated by cumulus cells. This mechanism involves LH and induces the disruption of communication between the oocyte and cumulus cells, thereby halting the flow of regulatory molecules into the oocyte. This induction is possibly mediated by the IP3/Ca2+ pathway.

Conclusion:-

Most of the articles in this systematic literature review use experimental design as their primary research method, where the subject has minimal impact on the method's efficacy and the researcher has strong control over the variables to obtain desired results. Nearly all articles in this research have indicated that the expression of LH receptor (LHR) is associated with LH, as LH cannot function without binding to its receptor, and the receptor needs to be expressed. Optimal expression of LHR with an optimal LH concentration will result in a higher oocyte maturation ratio, specifically at 10 µg/mL. Lower or higher concentrations of LH than the optimal concentration indicate lower oocyte maturation. Two out of ten articles have validated the highest expression of LHR is found in oocytes undergoing maturation, specifically in preovulatory follicles. Additionally, LHR expression also increases during the growth of antral follicles, especially at antral diameters of 8-10 mm, and this applies only to dominant follicles originating from normal cycles.

The addition of certain supplements can also affect LHR expression. An article shows that hCG supplementation can increase the percentage of mature oocytes at 12 hours post-injection with a predictive threshold value of 77 mIU/mL.Supplementation with FRBI can reduce LHR expression in COCs. The number of cumulus cells can also indicate the level of oocyte maturation, where oocytes completely covered by cumulus cells indicate the highest maturation.

Further research is needed on the role of LHR in fertilization, and on the supplementation/addition of other hormones that can enhance oocyte maturation. Furthermore, future research is needed on the role of LHR in oocytes derived from subjects with low ovarian response capacity.

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