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RESEARCH ARTICLE

RELEVANCE OF PHARMACOGEOMICS IN OVARIAN STIMULATION : A REVIEW

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Abstract

Genetic polymorphism is defined as the detection of a single genetic mutation in humans, and in addition each allele should occur at a rate of at least 1% of the population. Potential strategies for detecting various alleles related to specific diseases or responses to drug treatment include case-control studies in uninvolved and affected individuals or genome scanning techniques.Tailoring ovarian stimulation to the individual patient can be challenging because the ovarian response varies substantially between patients. Pharmacogenetics has emerged as a new area of research to improve the balance between desired and undesired actions of drugs, based upon the genetic predisposition of the individual patient. In summary, the use of genomic techniques may not be limited to the rapid and complete detection of drugs. The Ser680 in the gene FSH-receptor has been shown to cause low resistance and low response to FSH action in homozygous women (Ser680 / Ser680). The potential role of AMH in influencing the ovarian response in stimulation. Estrogen plays an important role in the development of secondary sex, fetal growth, the reproductive cycle, and the maintenance of pregnancy.

Introduction:-

Promoting the ovarian process reduces ovarian follicular growth and oocyte maturation using antiretroviral drugs. The stimulus can be used to create a normal menstrual cycle in protective women. Ovarian stimulation is a common process in assisted production and is used in combination with in vitro fertilization (IVF), intrauterine insemination (IUI) and other assisted living birth control techniques (ART).[1] In addition to preparing oocytes for retrieval, ovarian regeneration repairs a woman's uterus for implantation, by supporting growth of endometrial lining, the tissue where the embryo will implant if an egg is present.[2]

Ovarian stimulant is used to increase the strength of the endometrium wall in preparation for implantation of embryos, for women undergoing IVF 'thaw' cycles (meaning women have melted IVF embryos are implanted, so they do not need to receive a collection of oocyte), those implantation of fetal IVF donors and those acting as pregnancy agents. Medication promotion has now become a common practice throughout all Assisted reproductive technology(ART) cycles and over the years many drug kingdoms have been formed.[3]

Population variability does not include the possibility of a single control ovarian stimulation (COS) regimen that encompasses all patient needs. Modern technology has led to the development of new drugs, treatments, and computational methods that can pinpoint the characteristics of a single patient. This may be used to compare patients with appropriate treatment options to increase efficiency, safety , and tolerance during COS. At present, follicle-

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stimulating hormone (FSH) level remains the hallmark of a single patient most widely used in the clinic. These changes provide basic predictions of success and indicators of standard COS treatment according to the full patient categories. In contrast, the level of anti-Müllerian hormone appears to be an accurate predictor of ovarian storage and COS response and can be used effectively to regulate COS. it is necessary during recovery and successful treatment. Finally, in the future, genetic testing may allow each patient's response to regeneration during COS to be predicted based on genotype type. Unfortunately, despite the predictability of these measures, no single biomarker can stand alone as a guide in determining the best course of treatment. In the future, hormonal, active and genetic biomarkers will be used together to make COS your own [4][5].

Genetic polymorphisms

Differences between subgroups or individual patients are often caused by genetic polymorphisms in regions that include drug indicators, e.g. drug receptors, which form enzymes or transporter molecules. Genetic polymorphisms provide the basis for diversity and account for 85% of human genetic diversity. The human genome project has revealed that the human genome contains ~ 3 billion bases. To date, more than 1.5 million Single nucleotide polymorphisms SNPs have been identified, according to one SNP standard every 2000 bases (bp) [6]. Polymorphism, in contrast to abnormal mutations, in which it occurs more frequently> 1% in humans is called genetic variation. [7]. In addition to the SNP, polymorphisms can also be calculated in a simple sequence of polymorphisms or added and subtracted.[8] The phenotypic effects of SNP occurring naturally are not obvious, but can be seen after treatment modalities. The polymorphism in the FSH-receptor type is an example of how quality among people according to their genotype is clinically identified after a medical challenge[9][10]. Interestingly, follow-up studies in healthy women have shown that even without the challenge of medication, differences in receptor function can be detected by varying degrees of controlling the menstrual cycle.

Pharmacogenetics as a new approach to increase safety anddrug therapy Pharmacogenetics and pharmacogenomics

Individual diversity is one of the characteristics of human beings.Therefore, it is not surprising that drug responses given in the same way to certain individuals can vary greatly depending on side effects and clinical response or adverse events.

The simulation and development of therapeutic drugs in the genetic engineering of each patient emerged as the subject of a research novel to improve the balance between the necessary and unwanted actions of pharmacists.[11] This approach, called pharmacogenetics, has already been recommended as a future treatment solution for the media.

Pharmacogenetics defines the relationship between genetic drug response and genetic variation and also pharmacogenomics provides science in the study of the genome and its products - RNA and proteins - as related to human response to drugs. Finally, pharmacogenomics should be involved in the discovery and development of new drugs by better understanding and predicting patients' responses to drugs.[12]

Toxicity and drug use may depend on the recipient's genetic makeup. Since some people are influential and some patients are protected from side effects, pharmacogenetics can help boost the treatment window, e.g. by removing certain people at risk, or by adjusting the dose of the medical agent and thus improving the quality of treatment for a particular drug. [12]

Discovery of pharmacogenetic differences between individuals

Potential techniques for detecting various alleles associated with a specific diseases or responses to drug treatment include case-control studies for unaffected and affected individuals or genome scanning techniques. In case-control studies, alleles analyzed in different populations should be associated with genetic variation that can be manually linked to disease or the response of the drug being investigated. [13] For the example, with the difference of PCOS in the workplace of the androgen receptor may be involved in the clinical phenotype of this disease. Indeed, polymorphism of the androgen receptor gene with a short CAG sequence, which provides high activity on the written androgen receptor proteins was strongly associated withPolycystic ovary syndrome PCOS and may explain the more prominent androgenic sequence in PCOS compared to healthy controls.[14]

In contrast to the genetic approach, the different genetic regions associated with drug responses can be determined by examining the genomes of ‘case population’ compared to ‘human control’. This SNP two-person script analysis

strategy allows the creation of genomic regions that are more likely to be associated with disease or drug response than other regions. Thereafter, the region's genes and associated proteins can be identified and the suspected mechanisms can be confirmed to be effective in the future. [12]

Currently, many pharmacogenetic differences regarding the differences in pharmacokinetic and pharmacodynamic effects of drugs are known. It has been found that among standard studies, the activity of drug-induced enzymes can vary greatly and in vivo drug release levels can vary up to 40. Examples include the difference in hydrolysis, acetylation and oxidation. A well-known clinical example is glucose-6- phosphate dehydrogenase, which occurs in about 10% of black men. These subjects are at high risk of developing haemolytic anemia when given oxidant drugs, such as antimalarials. [15][16]

A common clinical example of pharmacogenetic variability leading to profound pharmacodynamics changes reduces warfarin activity in some patients, requiring warfarin dose up to 20 times greater than required. Decreased warfarin activity is most likely due to genetic reduction of the warfarin binding effect. [17]

Pharmacogenetics in ovarian stimulation

Pharmacodynamic variability in FSH treatment, due to genetic variation in patients with another example of FSH receptor polymorphisms. In summary, the use of genomic techniques may not be limited to the rapid and complete detection of drug. In most cases, it will be possible to diagnose patients genetically before starting treatment to improve the drug treatment window. Recognized genetic testing that affects drug action can provide the ability to adjust the dose of a drug for patients to benefit safely.

Pharmacogenetic approach in ovarian stimulation Candidate genes

Indeed, both genetic and clinical factors, first and foremost, contribute to the apparent divergence of follower recruitment and oocyte yield in ovarian stimulation cycles. The pharmacogenetic method of inserting genes into FSH volume to obtain the desired size of the ovarian response in COS is still in its infancy. To date, four polymorphic DNA markers on tested genes have been tested in clinical studies. Many studies address polymorphisms in exon 10 of the FSH-receptor type (p. N680S, p.T307A).(Simoni et al., 2002) In addition SNPs In the genes of the estrogen pathway, namely estrogen receptor alpha (ESR1, g. 938C → T), estrogen receptor beta (ESR2, 39A → G) and CYP19 fragrant gene (c. 1622C → T), linked to the effect of treatmentin the polygenic model, only FSH -receptor.[18][19]

P. The N680S polymorphism FSHR was strongly associated with a negative response phenotype after analyzing each sign separately. However, the authors have suggested that a polygenic model that incorporates FSH receptors, as well as ESR1 / ESR2 polymorphisms can accurately identify 10-15% of poor respondents in FSH treatment. This was the study of a fifth combination of genes to stimulate the ovaries to form a polygenic / oligogenic model, which could be used in the future to identify a different set of genes that regulate ovarian response to FSH.[19]

FSHR - Follicle-stimulating hormone receptor

The FSHR gene is found in chromosome 2 p21-p16 and contains 9 intrins and 10 exons. The first 9 exons contain a non-cellular receptor domain, while exon 10 contains the C-terminal end of a non-cellular domain, as well as the intracellular domain and the entire transmembrane domain of FSHR. Exon 10 is important for signal transmission, but it is not necessary to tie a ligand. To date approximately 1800 FSHR-type SNPs have been reported to the National Center for Biotechnology Information (NCBI). SNPs are located in encoding regions (exons, 8 SNPs), or in complex exon regions. Only 1 SNP is available in the 5 'uninterrupted region of FSHR mRNA - 29 (ss2189241). Of the eight SNPs in the codecs 7 are found in exon 10 codons 307, 329, 449, 524, 567, 665, and 680 codons. The last six SNPs eventually cause the synthesis of amino acids and therefore are not the same. The two most notable polymorphisms in terms of their structure and racial distribution are Ser680Asn (rs6166) and Ala307Thr (rs6165). Some of these polymorphisms are connected to each other during reconstruction in a way that always occurs together.

Several studies aim to link the study of FSHR polymorphism with ovarian function. A 680-level polymorphism that retains Serine residues in both alleles is associated with higher FSH serum filtration and longer phase length. This suggests that these FSHR variants are not sensitive to FSH. Indeed, women with Ser / Ser variability require higher FSH during their ovarian stimulation phase during IVF treatment cycles. In addition, the Asn680Ser polymorphism

was not associated with premature ovarian failure (POI). Finally, in women with PCOM the distribution of these two allelic species differed significantly between different studies. [20][21][22]

Resistance of the homozygous Ser680/Ser680 allelic variant of the FSH receptor to FSH action

The genotype of the amino acid Ser in codon 680 of the FSH-receptor gene has been seen as creating a low resistance and low response to FSH action in homozygous women (Ser680 / Ser680). Basal FSH has been reported in general studies of patient maturation and transplantation[9] of patients [21][22] with this type of natural medicine with significant focus. Indeed, randomized clinical trials were in line with the notion that the increase in FSH required to overcome partial FSH receptors associated with this particular genotype by secretion of oestradiol granulosa cells: compared to the 'wild' type Asn680 / Asn680 those with Ser6 strains Ser680 allelic require a very high dose of FSH that will be used to stimulate IVF ovarian to achieve the same combination of oestradiol on the day of administration of chorionic (HCG).[9] Other retrospective studies were also associated with this concept. [21][19][23][22][24] The reported reduction of oestradiol and baseline FSH concentration in these studies suggest that the Ser680 / Ser680 type is more 'resistant' to FSH action, and therefore requires greater intensity of the same natural response, which can lead to higher FSH levels in women with this different problem.[25]

LH - *Luteinizing hormone polymorphism*

The LH receptor type is known to carry as many as 282 SNPs.[26] In 1991, Söderholm and Patterson identified common genetic similarities of alterLH or LHβ or as a result of two mutations made on a polymorphic basis in the type of subunit that led to the amino acid sequence, Ile15Thr and Trp8Arg et al. Initially they suggested that this be found to be a debilitating LH form. [27]

The short life span of v canLH can be linked to the presence of additional signal glycosylation in a subunit that can lead to the addition of a second oligosaccharide to Asn13 β protein. It was found that there is a greater chance of normal LH activity of v βLH in the reception area; however, its length is shorter in vivo [28] Previous clinical trials designed to determine the effect of this variant on reproductive health have reported its association, premature ovarian failure, ovulatory disorders, hyperprolactinemia, menstrual disorders, luteal dysfunction, endometriosis and infertility. [29] resulting in a high demand for r hFSH (> 2500 IU).[28] In one of the first studies, the complete use of r hFSH was elevated during ovarian stimulation due to the presence of v βLH. Based on the findings, the researchers demonstrated the potency of v βLH as a sign of ovarian response to r hFSH. This role of v βLH, if confirmed by further research, can thus enable clinicians to identify patients who require abnormal LH supplementation during ovarian stimulation. [28]

Role of luteinizing hormone

LH supplementation is important in elderly and poor responding patients because they usually receive high doses of FSH for COS, which show high levels of progesterone at the end of stimulation and after that, their endometrial reception decreases. [30][31]

***AMH* gene polymorphisms**

AMH polymorphisms, found in 19p13.3, [19p13.3, MIM 600957, Genebank ID 268], and its receptor AMHR2 [12q13, MIM 600956, Genebank ID 269] with estradiol levels during the menstrual cycle phase. , which raises the role of FSH sensitivity control. [32] Therefore, genetic variation in the genes of AMH and AMHR2 can affect the action of hormones in folliculogenesis, leading to infertility.

Rigon et al. [33] investigated AMH and AMHR2 polymorphisms in women with idiopathic infertility and found that genotype distribution differed significantly between cases and controls. Riggs et al. [34] it has been shown that AMH can mark the ovarian response, provide assistance in the selection of donors, and may also predict ovarian hyperstimulation syndrome. Earlier, these authors showed that AMH was also associated with ovarian storage and the number of oocytes detected, and therefore had a higher predictive value in terms of age, hormonal levels of FSH, LH, estradiol and inhibin B. [35]But- then, AMH polymorphisms affect the functions of biological hormones, which play an important role in regulating the formation and formation of follicles.[36] A study of the genetic polymorphism that regulates female reproductive function may help to determine the mechanisms responsible for gonadal function and reproduction in humans.[33]

Based on these findings, we aimed to test the G146T / Ile49Ser / rs10407022 polymorphisms of the AMH gene and A-482G / rs200255, A10G / rs11170555, C1749G / rs2071558 and G4952A / rs374azil616 for R2 , and correlated

the findings with AMH, FSH and estradiol serum levels, response to ovarian hyperstimulation (COH) and assisted reproductive effects (e.g. maturation), embryos produced, transfer of embryos, frozen embryos and pregnancy rate).

AMH as a marker for ovary stimulation

The potential role of AMH in influencing the ovarian response in regeneration, it has been suggested that genetic variation involving the signaling pathway of AMH may affect ovarian response during ovarian stimulation (COS). [37] The AMH type is located in the short chromosome 19 and has 5 tests. On chromosome 12 and it contains 11 genes, the gene AMHR2 is found. Many polymorphisms related to these two genes have been studied. Polymorphisms AMH c. 146G> T, p. 49Ser (rs10407022) and AMHR2 -482A> G (rs2002 555) have attracted a lot of attention. [38]

The AMH rs10407022 polymorphism resides in the promotional region. This polymorphism leads to the conversion of serine isoleucine which replaces 49 AMH proteins, and can affect AMH function.[39] The AMHR2 rs2002555 polymorphism is in the non-encoding area of the promoter, and may affect the AMHR2 transcription process. Several studies focused on these two polymorphisms and suggested that these two genes were associated with higher estradiol levels in androgen, follicle number, unexplained infertility and normo-ovulatory women in polycystic ovary syndrome (PCOS).[40] Another study investigated the effects of these two polymorphisms during COS on rehabilitation technology (ART).

However, the results of these studies were inconsistent. Meta-analysis of polymorphism AMH (rs10407022) was published. However, this study only examined the relationship between reproductive effects in Caucasian populations and AMH polymorphism. [41] Since then, several new studies have been published in the SNPs of the AMH / AMHR2 method. For this reason, we feel it is important for clinicians to perform meta-analyzes to fully analyze the role of AMH (rs10407022) and AMHR2 (rs2002555) in ovarian response and the effects of in vitro fertilization (IVF) during the ovarian stimulation process.

Estrogen receptor genetic polymorphisms

Estrogen receptors (ESRs) are important partners in the ovarian response to FSH, because the direct effects of estrogens on follicle growth, maturation and oocyte release are well established.[41] In addition to folliculogenesis, estrogens play an important role in regulating endometrial implantation. [42] Estrogen signaling is mediated by estrogen receptors, which are ligand-binding compounds that are made up of a number of important hormones that bind to hormones, bind DNA, and bind to text.[43]

Two estrogen receptors have been identified in humans, ERa (6q25) and ERb (14q22), produced by the genes ESR1 and ESR2, respectively. In folliculogenesis, the increase in the action of estrogens is controlled by ERa (usually expressed in the theca layer), and the differences and effects of inhibition required to reach the antral stage require ERb (expressed in growing granulosa cells). [44][45] follicles at all stages of growth; Previous findings have shown that genetic variation in ESR genes is involved in the effect of ovarian stimulation [46][18][19][47]. In fact, the fifth pharmacogenetic method used in COH / IVF in 1997 focused on the polymorphisms of ESR1gene. [46]

The ESR1 type is high polymorphic, with more than 2200 SNPs, while about 720 SNPs are identified in ESR2. The most common polymorphisms studied in ESR1 are rs2234693 T / C, expressed by the purifying enzyme PvuII and rs9340799 (A / G, defined by the enzyme XbaI inhibitor) at intron 1 and (TA) I have a replicating nucleotide polymorphism in the regional promoter. The PvuII TT type is associated with decreased pregnancy rates for women receiving IVF, in which 2 to 3 consecutive cycles are studied. [46][18] In some studies, when single cycles were followed, no effect of ESR genotypes on pregnancy levels was found. These results point to the effect of ESR1 PvuII polymorphism on the resulting pregnancy that led to COH / IVF, rather than transmitting it to a single embryo. [47][47][48] In conjunction with PvuII TT and declining pregnancy rates, IVF patients carrying the PvuII CC genotype show an improved number status, with higher number of follicles, [46]mature oocytes, pregnancy rate and appropriate embryos following COH / IVF.[18][47][49]In addition, we found a long-term and long-term relationship between C and TA, and as a result there was a better COH response.[47]

In addition, the frequency of residual PvuII C was found to be lower among the poorest respondents (≤3 follicles) compared with normal COH responders. [19]Another common SNP in the ESR1 gene, XbaI A / G, also showed a correlation with the COH effect: [49](oocyte maturation and pregnancy rates were higher in women with the XbaI GG genotype. In addition we have shown an association between type GG genotype and higher estradiol levels

obtained during COH. [47]Previous research by de Castro et al. the team presented the first multilocus analysis, in which the oligogenic model of FSHR 680Ser - ESR1 PvuII T - ESR2 AluI G described a negative response to FSH in COH.[19] The result of this analysis can be seen because, obviously, the negative impact on the marking method will not prevent the involvement of the selected gene.[50] In fact, the same study with our previous genetic study did not produce any effect of ESR2 RsaI G / A and AluI G / A[47]polymorphisms on the COH effect. Taken together, these documents support the notion that estrogen signaling pathways play a role in the COH effect. [19] However, more comprehensive and independent analysis has used a larger sample size, with other people needed to confirm or refute prior recognition.

ESR role

The gene Estrogen receptor (ER) plays a major role in oocyte maturation, folliculogenesis and pregnancy. Therefore, the current study was aimed at investigating ESR polymorphisms in groups of women who did not experience in vitro pregnancy (IVF) with ovarian reserve in ovarian hyperstimulation (COH) controlled by follicle-stimulating hormone (FSH).

Estrogen plays an important role in the development of secondary sex, fetal growth, the reproductive cycle, and the maintenance of pregnancy. [51] In addition, estrogen regulates endometrial cell division and regeneration. [52] ER is divided into beta (ER) and alpha (ER) types. In research, removing beta receptors in mice leads to lower egg production and ultimately infertility, due to decreased ovarian tissue. [53] In another study of ER gene knockout mice, it was confirmed that ER is important for egg maturation in general but not for sex segregation, reproduction, and time period. [54]

The genetic significance of the active ESR2 +1730 G / A polymorphism is unclear as it does not lead to amino acid conversion to ERprotein. However, it is possible that polymorphism is associated with other regulatory sequence changes that may affect genetic expression and its function. [52]Newer, more focused on your own treatment. The patient's pharmacogenetics are important in the treatment of diseases, so depending on the patient's medication in the body, medication and dose are determined. Therefore, in obstetric treatment, the patient's genetic effects in response to treatment should be considered. According to the studies we have listed, it has been shown that ESR2 +1730 G / A polymorphism plays a role in egg maturation and we have chosen a polymorphism to review its effects on IVF outcomes. To study the role of genetic response in the treatment of non-infectious patients in this study, the ESR2 gene +1730 G / A polymorphism role was evaluated in response to the treatment of 91 infertile women. When considering the need to remove the confusing material from these patients to study the genetic effects in response to treatment, infertility patients associated with male characteristics and excluded endometriosis. Also, because the purpose of this study was to test the response of a different polymorphism in the treatment of non-infectious patients, general cases were not considered. In the study of Seleem and colleagues, GG type was more common than other genotypes, while in the present study, the frequency of GA genotype was higher than in other genotypes. This difference may be due to racial differences in the two groups or the sample number. [53] To evaluate patients' response to treatment in this study, the number of follicles and egg number after ovulation stimulation and egg rate.

Ovarian response to in vitro fertilization cycles and estrogen receptor beta + 1730 polymorphism in follicles were considered. This measure is important in the sense that some strings can have nothing but an egg. The results of the egg measurement from the follicles in all groups were similar. Therefore, there was no significant difference; however, in the present study, the number of follicles in the GA group was large, but this difference was statistically significant. Overall, in the present study, the GA group received the highest percentage of pregnancy (25.4%) while the AA group was the lowest (20%). Although there were no similar studies in this region to the best of our knowledge, we can look to the Sheikh and our partner research on the type of ER alpha which showed that 40% of the heterozygote Pp group had a very successful pregnancy and the lowest pregnancy rate in the pp group was 20%. Therefore, the highest responses in the treatment of both subjects were in the heterozygous genotype group. Regardless of the success of IVF, estrogen levels should be low, and small or large amounts will have a negative impact on the treatment response.

Conclusions:-

After decades of IVF techniques, the availability of new markers of ovarian reserve could open a new scenario field. While many years ago the dosage was guided only by anthropometric(BMI, age), today the availability of more specific markers could significantly ameliorate IVF outcomes leading from a “one size fits all’’ a “patient tailored”

approach. In the future, the use of specific genetic tests (such as and Ser680 variant of FSH-R) might lead approach to COS.

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