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THE OVERVIEW AND ROLE OF HEAT SHOCK PROTEINS (HSP) ESPECIALLY HSP 60 AND 70 IN REPRODUCTION AND OTHER PATHOLOGIES (a literature review)

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Abstract. The overview and role of heat shock proteins (HSP) especially HSP 60 and 70 in reproduction and other pathologies (a literature review). Berestoviy V.O., Ahmad Mahmood, Venckivska I.B., Ginzburg V.G., Sokol I.V., Berestoviy O.O., Govsieiev D.O. *A search of peer-reviewed articles regarding heat shock proteins (HSP's) especially HSP 60 and 70 was conducted in this review to understand its role in the development of various complications like miscarriage, preterm birth, tubal infertility and spontaneous abortion associated with chlamydial HSP 60 in IVF, male infertility, preeclampsia, cancer, immune system activation, autoimmune diseases, coronary heart disease, dysregulation of steroidal hormone from the endometrium and its up-regulation in stress response. ELISA, western blotting, immunofluorescence, and affinity chromatography were the most common methods researchers used to determine and separate HSP 60 and antibodies related to it. Heat shock proteins are responsible for normal folding of other proteins and prevent its abnormal folding and cause degradation of abnormally folded proteins, mitochondrial*

protein transport, DNA metabolism, regulation of apoptosis are their significant functions. HSP 60 is a homologue of bacterial HSP 60 (GroEL) and needs co-chaperonin HSP 10 for its proper functioning. Gynaecological and obstetrical complications were more prevalent in most studies. Pregnant women were mostly affected subjects. Abnormal HSP 60 leads to a high level of unfolded or misfolded proteins, which in turn activate other body systems to produce the clinical outcome. Some researchers stated that there is no association between preterm birth and HSP 60 & 70, chlamydial HSP 60 antibodies trigger tubal infertility, preeclamptic pregnancies has detectable HSP60 as compared to control, GroEL leads to tubal infertility and IVF failure, chlamydial (CHSP 60) activates autoimmunity. HSP60 seropositivity reduces the opportunities of ectopic pregnancy, levels of HSP 60 does not stay constant throughout the menstrual cycle in reference to control, while other opposed these conclusions in their research works. According to some researchers, HSP 60 is a risk factor for pregnancy-related pathologies development, and some other opposed this theory and considered HSP 60 as a safety factor for normal pregnancy outcome, according to this review harmful effect of HSP 60 dominate, in future further high-quality studies need to be done for better understanding.

Реферат. Визначення ролі білків теплового шоку (HSP 60 і 70) в репродукції та в розвитку інших патологій (огляд літератури). Берестовий В.О., Ахмад Махмуд, Венцківська І.Б., Гінзбург В.Г., Сокол І.В., Берестовий О.О., Говсєєв Д.О. *У цьому огляді було проведено пошук рецензованих статей щодо білків теплового шоку (HSP), особливо HSP 60 та 70, щоб зрозуміти його роль у розвитку різних ускладнень, таких як: звичне невиношування, передчасні пологи, трубне безпліддя, спонтанний аборт, безпліддя, що потребує застосування ДРТ, чоловіче безпліддя, прееклампсія, онкологічні захворювання, гіперактивація імунної системи та автоімунні захворювання, ішемічна хвороба серця, порушення регуляції стероїдних гормонів та регуляція відповіді на стрес. ІФА, вестерн-блот, імунофлуоресценція та афінна хроматографія були найпоширенішими методами, які дослідники використовували для визначення та відокремлення HSP 60 та пов`язаних з ним антитіл. Білки теплового шоку відповідають за: нормальний фолдинг інших білків і запобігають їх аномальному згортанню, відіграють роль у деградації аномально складених білків, транспорті білків із мітохондрій, метаболізмі ДНК, регуляції апоптозу. HSP 60 є гомологом бактеріального HSP 60 (GroEL) і потребує ко-шапероніну HSP 10 для нормального функціонування. Аномальний рівень HSP 60 призводить до порушеного фолдингу, що, у свою чергу, є причиною некоректної конформації та функціонування білків, що призводить до клінічних проявів захворювань. Деякі дослідження вказали, що немає зв`язку між передчасними пологами та HSP 60 і 70. Антитіла до хламідійного HSP 60 викликають оклюзію маткових труб, призводять до виникнення прееклампсії, також рівень HSP 60 не залишається незмінним протягом усього менструального циклу, тоді як інші виступали проти цих висновків у своїх дослідницьких роботах. На думку деяких дослідників, HSP 60 є фактором ризику розвитку патологій, пов'язаних з вагітністю, а деякі інші виступали проти цієї теорії і вважали HSP 60 фактором безпеки для результату вагітності, згідно з цим оглядом шкідливий ефект HSP 60 домінуватиме, але в майбутньому для кращого розуміння потрібно провести подальші дослідження.*

Abbreviations. Heat shock proteins 60 (HSP 60), chlamydial (CHSP 60) heat shock protein 70 (HSP 70), in vitro fertilization (IVF), enzyme-linked immunosorbent assay (ELISA)

Heat shock proteins are responsible for preventing proteins damage in response to high levels of heat. Heat shock proteins are classified into six prominent families based on their molecular mass: small HSPs, HSP40, HSP60, HSP70, HSP90, and HSP110 [22, 32]. Heat shock proteins (HSPs) are phylogenetically conservative proteins, wich usually considered to be intracellular proteins with molecular chaperone and cytoprotective functions [27]. Furthermore, the amino acid sequence showed strong homology between HSP60 and GroEL. Firstly, HSP60 functions only in the mitochondria and that there was no alike protein located in the cytoplasm. Later discoveries have discredited this claim and have suggested a recognizable difference between HSP60 in the mitochondria and the cytoplasm [25]. Mutagenic investigations have also revealed the HSP60 association in replicating and transmitting mitochondrial DNA [14]. The cytoplasmic HSP60 structures a complex with proteins responsible for apoptosis and controls the action of these proteins. The cytoplasmic adaptation is additionally engaged with insusceptible reaction and cancer [25].

The Aim – The basic purpose for this review was to analyze libraries (Google scholar, Pubmed, web of science, Cochrane library), and understand the basic structure, functioning and how the heat shock proteins especially HSP 60 and 70 play a role in the development of different pathological conditions, and also to clarify that the presence or absence of heat shock proteins has beneficial effects or harmful effects in terms of reproduction and other clinical conditions.

Role of HSP 60 and 70 in different conditions

1. Stress response

HSP60, as a mitochondrial protein, has been demonstrated to be associated with a stress reaction. The heat-shock reaction is a homeostatic system that shields a cell from harm by its up-regulation [10,

28]. In one analysis, examiners treated different mice with L-DOPA and found significant upregulation of HSP60 expression in the mitochondria and HSP70 expression in the cytoplasm. Scientists presumed that the heat shock signal pathway fills in as "the essential component of barrier against neurotoxicity evoked by free extreme oxygen and nitrogen species created in maturing and neurodegenerative disorders [20]. Several examinations have indicated that HSP60 and other heat shock proteins are vital for cell endurance under harmful or distressing circumstances [2].

2. Miscarriage

Unconstraintly, preterm delivery remains ponderable complication in obstetrics. There is a proof recommending a relationship between raised HSPs in pregnancy in premature delivery. Accessible proof is more for HSP70 [34]. The women with miscarriage detected with antibodies to CHSP60 compared to the women without any history of miscarriage, measurement of human HSP60 can be a forecasting parameter for chlamydial induced miscarriage [35]. Furthermore, HSP 70 also can assess the miscarriage in the first semester of pregnancy [38]. It appears that this expansion is partially recipient for the hatchling since this HSP70 intervenes some portion of the down-regulated versatile immunological reactions prompting the insusceptible resilience of the baby. After a specific edge of increment, this HSP70 may injure and lead to unnatural birth cycle or premature birth through the hindrance of autophagy [34]. Results set for the investigation of the examination was to reflectively analyze the serum levels of HSP60 and HSP70 between ladies who lost versus those who did not. To end-up with this examination, a sifting procedure was applied. As per this, all ladies who inevitably prematurely delivered were chosen. Pregnancy loss was characterized as pregnancies that finished in an unconstrained fetus removal before the initial 20 weeks of gestation [7]. The relationship of a dysregulation somewhere in HSP60 and HSP70 originates from three clinical investigations. Coursing IgG antibodies to the human HSP60 and HSP70 were estimated in 68 ladies with repetitive pregnancy loss and contrasted and 29 pregnant controls. Fixations were more prominent in ladies with repetitive premature births than normal pregnancies. In any case, no noteworthy connection could be found between these records and the coursing IgG antibodies against HSP60 and HSP70 [26].

3. Preeclampsia

HSP60 mRNA levels in maternal entire fringe blood separated between specific complications. While maternal hypertension did not affect HSP60 mRNA levels, the event of preeclampsia or potentially fetal development confinement demonstrated the expansion of HSP60 mRNA levels in the maternal course. HSP60,70 mRNA levels were expanded in maternal dissemination during the beginning of mild preeclampsia, severe preeclampsia, and fetal development confinement. All things considered, the most unusual maternal stress reaction (the most significant levels of HSP60 mRNA) was seen in pregnancies with indications of the centralization of the fetal course, which is profoundly connected with the fetal hypoxia [4]. Furthermore, the concentration of serum HSP 70 found high in women with a history of preeclampsia compared to control and maybe it is a cause of preeclampsia development [9, 33]. Other studies opposed this conclusion and stated that there is no association of HSP70 with preeclampsia and eclampsia [5].

4. Coronary heart disease

Concentrations of supplement initiating antihuman HSP60 antibodies yet not add up to IgG hostile to HSP60 and antibodies are autonomously connected with high familial risk for coronary illness in sound children [6]. In a past report, the strange dealing of HSP60 to the cell surface was proposed to be an early trigger for myocyte failure and the movement of cardiovascular breakdown [17]. Furthermore, HSP plays a role in developing atherosclerosis and essential hypertension by triggering and activating the autoimmunity [31]. Counteracting agent levels to entire HSP60 and HSP65 were not related to type 1 diabetes mellitus in youngsters, while antibodies to certain epitope areas on HSP60 were recognized in high titers in kids diseases [1].

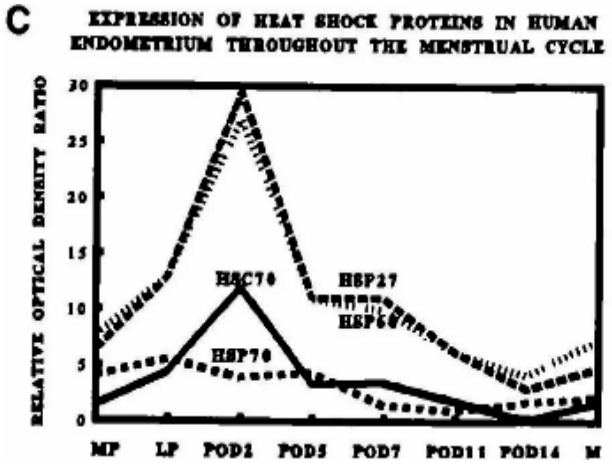
5. Male infertility

Male immunity to CHSP60 does not impact semen quality and sperm functional capacity [8]. In response to intrinsic or extrinsic heat stress, the high level of HSP 70 produced and interfered with normal autophagy function, leading to a decrease in the quantity of functional ova and spermatozoa [34]. Further investigations are essential to clarify the low degree of HSP60 creation in seminiferous epithelia with spermatogenic absconds. Explanation of this inquiry might help determine and comprehend male infertility and protective effects [40].

6. Effect on the endometrium

The human endometrium is a steroid-delicate tissue, and there is proof that supports the perspective that heat shock proteins (HSP) are embroiled in the guideline of steroid work. Subsequently, the outflow of different individuals from the heat shock group of proteins in the steroid-responsive human endometrium. When standardized to the sum HSP

the expression, HSP60 expanded continuously during the late proliferative and early secretory stages and decreased in the mid-to-late secretory and menstrual stages (Fig.). Interestingly, the inducible type of heat shock protein 70 (HSP70) did not experience these changes. These proteins' cell and subcellular confinements were analyzed in human endometria by immunohistochemical recolouring, except for HSP70, which was found principally in the epithelial cells. The immunoreactivity for other heat shock proteins was found in both the stroma and the epithelium. Immunoreactivity for HSP27 and HSP 60 was found in the lymphoid totals inside endometrial stroma, and both HSP27 HSP 60 were found in endothelial cells [36].



The expression of heat shock proteins throughout the menstrual cycle

7. Immunological role

The HSP60 has commonly been known as a chaperonin which aids protein folding in mitochondria. Some new research demonstrated that HSP60 potentially assumes a role in a "peril signal course" immunological response [13]. Infection and illness incredibly dysregulate the cell functioning. When a cell is under stress, it usually builds the generation of stress proteins, including heat shock proteins, for example, HSP60. With the end goal for HSP60 to go about as a sign, it must be available in the extracellular condition. In ongoing exploration "it has risen that… chaperonin 60 can be found on the outside of different prokaryotic and eukaryotic cells, and can even be discharged from cells [29]. According to late research, a wide range of sorts of heat shock proteins are utilized in safe reaction flagging, yet various proteins act and react distinctively to other atoms. HSP60 has been demonstrated to be discharged from explicit cells like fringe blood mononuclear cells (PBMCs) when there are lipopolysaccharides (LPS) or GroEL present. This proposes that the cell has various receptors and reactions to human and bacterial HSP60. Likewise, it has been indicated that HSP60 can actuate monocytes, macrophages and dendritic cells, and of initiating discharge of a broad scope of cytokines [12]. There is in any case, a curve in the immunological job of HSP60. As referenced above, there are two distinct sorts of HSP60 proteins, bacterial just as mammalian. Since they are fundamentally the same as in succession, bacterial HSP60 would not be required to cause a huge immunological reaction. The immunological framework is "intended to disregard self', that is, have constituents; in any case, incomprehensibly, this is not the situation with chaperonin. It has been discovered that numerous competitor of chaperonin antibodies exist and are related to numerous immune system problems. As per Ranford, et al. tests have been performed which have demonstrated that antibodies which are "produced by a human host after a presentation to bacterial chaperonin 60 proteins can cross-respond with human chaperonin 60 proteins [29].

8. Autoimmunity

Horvath et al. did not discover any distinctions in the counter HSP60 antibodies fixations between patients with foundational lupus erythematosus (SLE), RA, fundamental sclerosis, ankylosis spondylitis and controls, however, discovered raised levels just in undifferentiated connective tissue disease [11]. Interestingly, Yokota et al. discovered an expanded recurrence of HSP 70 in osteoarthritis [30], HSP60 autoantibodies in SLE, RA, and blended connective tissue problems, not in Sjögren's disorder. Nonappearance against HSP60 reactivity in the last issue was affirmed by others [24]. Women experiencing in vitro fertilization (IVF) never acknowledged they had a chlamydial infection yet were sure for cervical anti chlamydial immunoglobulin (IgA) antibodies had a much lower pregnancy rate than the ladies who were negative for these antibodies. Moreover, cervical IgA antibodies to the chlamydial HSP60 are similar to an engineered peptide compared to HSP60. Epitope present in both the chlamydial and human HSP60 likewise corresponded with IVF failure. Hence, autoimmunity to HSP60 may build defenselessness to beginning time pregnancy loss [39].

9. Infertility due to chlamydial immune response to HSP 60

Chlamydia trachomatis is a bacteria that can arise from the cervix to the fallopian tubes and may be asymptomatic for a long time. The insusceptible reaction to disease clears the extracellular organism prompts the growth of intracellular infection [13].

Repeated cycles of infection actuate tubal block and infertility. The infected cells keep on incorporating the chlamydial 60 KD heat shock protein (HSP60). Insusceptibility to moderated points of HSP60 may bring about autoimmunity to human HSP60. Expression of HSP60 by the embryo and decidua during early pregnancy may reactivate HSP60-sharpened lymphocytes, affect the normal pregnancy by actuating the insusceptible immunological components, and lead to resistant of the growing embryo. Maybe because of this, ladies with tubal infertility who are susceptible to the human HSP60 may have less effective result after experiencing in vitro treatment and successful embryo transfer [3].

10. Relationship to cancer

HSP60 has appeared to impact apoptosis in tumour cells related to an adjustment in expression levels. There is some irregularity in that some examination shows a positive expression while other research shows a negative expression, and it appears to rely upon the kind of malignant growth. There are various theories to clarify the impacts of positive versus negative expression. The positive expression appears to restrain "apoptotic and necrotic cell demise", while is thought, negative expression have to an influence "in actuation of apoptosis" [37]. As for impacting apoptosis, HSP60 changes in expression level have been demonstrated to be helpful new biomarkers for analytic and prognostic purposes [16]. According to Lebret et al., lost HSP60 expression shows a poor visualization and the danger of creating tumour penetration, explicitly with bladder carcinomas; however that does not remain constant for different kinds of cancers [11]. For instance, ovarian tumour explorers have indicated that overexpression is related to superior anticipation, while a diminished expression is associated with an aggressive tumour [15]. The chlamydia trachomatis was detectable in the ovarian tumour, indicating that it may be a carcinogenic agent, but there was no association between chsp60 and ovarian tissue with any ovarian subtype tumour [21]. All this exploration demonstrates that it might be feasible for HSP60 expression to be utilized in foreseeing endurance for particular sorts of malignant growth and along these lines might have the option to recognize patients who could benefit by specific treatments [18].

11. Spastic paraplegia

The absence of HSP60 in microscopic organisms, yeast or chloroplast, is deadly, and change in HSP60 quality is responsible for inherited spastic paraplegia [23].

12. Role in ectopic pregnancy

Subjects with previous chlamydial infection seropositive to hHsp60 have fewer chances of ectopic pregnancies development [32].

Our primary concern for this review was to analyze HSP60,70-related to gynaecology and reproductive immunology, and we also reviewed their other roles like in immune system activation, preeclampsia, in development of cancer and immunological roles like cell-mediated immunity and autoimmunity. Our study indicates that HSP 60,70 is one of the risk factors for developing pregnancy-related pathologies. It can be clinically implicated among the essential elements for screening pregnancy tests, unlike other diseases, leading to reproducing relevant pathologies. The prophylactic dimension of antibodies to human and bacterial HSP 60 and 70 can give the info for forecasting the normal reproductive outcome. The majority of genital chlamydia and also other infections in women are asymptomatic. Undetected and neglected, these infections can rise right into the top genital system and trigger PID (pelvic inflammatory disease) with the resultant development of reproductive pathologies [19]. Many research studies have shown that many females with HSP60 antibodies experience adverse reproduction result. Even without a straightforward solution to the reason the and-effect relationship between HSPs and linked pathologies, elevating the awareness of HSP 60,70 as a serological parameter in the gynaecology and obstetrics. Timely referral to gynaecological treatment and organized assessment of human and bacterial HSPs in females might make certain timely diagnosis and treatment of disabling gynaecological conditions and develop a possibility for accurate tracking and early intervention among risky expectant ladies.

Research can be implicated as different scientists' statements about HSP 60,70; some conclude it is essential components for the maintenance and survival of normal reproduction, and others opposed this theory and stated that it causes harmful consequences. So further studies need to be done for better understanding of the role of HSP 60,70. The quantity of heat shock proteins is equitable to analyze and prevent its harmful consequences, especially in women during pregnancy. Further studies need to analyze that either HSP 60 dysregulation has harmful consequences or triggers and activates our body's other systems to cause harmful consequences. Many scientists have done works on HSP 60 associated conditions, but there is also need to determine the normal level of HSP 60 in all three trimesters, and we did not found any work on this measurement so in future studies it needs to be explored. In future, the development of some antibodies or some hormonal chemical substances discovery will able us to develop some control on HSP 60,70 induced harmful consequences so that

the level of HSP can be controlled,i.e. inhibited or increased by using these chemical substances, further studies needed to do on this parameter.

CONCLUSION

According to some scientists, HSP 60,70 is a danger variable for reproduction-related pathologies, and a few others opposed this concept and considered HSP 60,70 as a risk-free variable for the regular reproductive outcome. According to this evaluation, unsafe HSP 60,70 dominates, although even more high-quality research must look at the elements responsible for these risks. Analysis of antibodies to HSP 60 and HSP 70 allows increased fetal surveillance and mother's wellness and, likewise, an ideally enhanced subsequent reproductive result. The risk of reproductive pathology growth increases as the level of HSP 60,70 changes. We have learned from this review that HSPS 60,70 plays a role in disturbance of normal physiological function and leads to some unfavourable clinical consequences it affects both genders, but pregnant women's are at more susceptible to these risk of HSPs has close relation with gynaecology and obstetrics. According to the previous work, demographical factors changes have little influence on these heat shock proteins' expression. In pregnant females, tubal infertility, autoimmunity, miscarriage and preeclampsia development was most prevalent, and in the male, it leads to male infertility.

Conflict of interests. The authors declare no conflict of interest.

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