Journal of Basrah Researches (Sciences) **50**(2), 77 (2024)
DOI: https://doi.org/10.56714/bjrs. 50.2.7

Assessing the Potential of Mainstream Pregnancy-Associated plasma protein A (PAPP-A) Level in Men as a Biomarker for Fertility: A review

Zena Saleem Zamil[1, *], Marwa Mahmood abduulraheem[2], Ghufran Mahdi Khaleel [3] Shams Khaleel Ibraheem [4]

[1] Department of Pharmacology and Toxicology, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.
[2]. Applied embryology, collage of medicine, Tikrit University, Tikrit, Iraq.
[3] Al – Nahrain university college of medicine, Department of human anatomy, Baghdad, Iraq.
[4] Pharmacology & Toxicology, Collage of pharmacy, University of Mustansiriyah, Baghdad, Iraq.

ARTICLE INFO

Received 14 May 2024
Revised 31 August 2024
Accepted 17 September 2024
Published 31 December 2024

Keywords:

PAPP-A, Male fertility, Sperm Quality, Predictive Biomarker, Reproductive Disorders.

Citation: Z. S. Zamil et al., J. Basrah Res. (Sci.) **50**(2), 77 (2024).
DOI:https://doi.org/10.56714/bjrs. 50.2.7

ABSTRACT

Background As a measure of a man's fertility, PAPP-A levels have lately been in the spotlight. Although most studies have focused on its role in pregnancy issues such low birth weight and gestational age, its potential impact on male fertility is starting to get more attention. Aim to determine if it is possible to use the levels of pregnancy-associated plasma protein-A (PAPP-A) in men's blood as a biomarker. The study's goal is to learn more about these levels' prognostic power and clinical assessment use by looking at the correlation with reproductive indices. Results Although there is a lack of evidence linking PAPP-A to sperm quality, there is some evidence that PAPP-A levels are associated with male reproductive problems. Future studies should look at the possibility of a stronger link between PAPP-A and male infertility. As a predictive biomarker, PAPP-A has a number of limitations when compared to other, more established fertility indicators like VAP-1. To summarize more study is needed to establish the reliability and therapeutic value of PAPP-A, while preliminary results indicate its promise as a biomarker for male fertility prediction. It will be vital to this effort to understand the possible pathways that link PAPP-A to male fertility. So, it's necessary to dig more into the link between PAPP-A levels and male infertility. As a conclusion: PAPP-A levels must be compared to other biomarkers to predict male fertility.

***Corresponding author email :** zeena90@uomustansiriyah.edu.iq

ISSN: 1817-2695 (Print); 2411-524X (Online)
Online at: https://jou.jobrs.edu.iq

1. Introduction

Pregnancy-associated plasma protein-A (PAPP-A) is a regulatory protein in the insulin-like growth factor system, firstly identified as placental protein, later on they found that it presents in both male and female serum including pregnant and non-pregnant women. Also, it presents in the follicular fluid and in the culture media of early developed embryo.[1]

Insulin-like growth factor plays a vital role in tissue growth by their interactions with its receptors and insulin. There are six binding proteins, IGFBPs 1 to 6 that regulate the activity of IGFs by binding to their receptors. However, IGFBPs also impair productive binding of IGFs to their receptors, so proteolytic proteins are required for IGF signalling to occur by degradation of IGFBPs.[2]

There are two main biochemical structure, PAPP-A and PAPP-A2, both are metalloproteinases.[3]PAPP-A have a proteolytic activity on IGFBP2, IGFBP4 and IGFBP5, mainly IGFBP4 while PAPP-A2 regulates IGF1 activity by cleavage of IGFBP3 and IGFBP5.[4]

PAPP-A have an effect on cell differentiation, proliferation, migration, and survival. They also have a significant effect on several reproductive functions, including oogenesis, development of ovarian follicles, oocyte maturation and ovulation, follicular atresia, luteal function and testicular function. The disturbance of this axis to pathological conditions like anovulation, female infertility or implantation failure, in addition to male infertility. [5] Therefore, the levels of circulating PAPP-A have been linked to various male reproductive disorders, making it a potential biomarker for assessing male fertility. [6][7]

Twenty percent to thirty percent of infertility cases are caused by male factors, accounting for fifty percent of all instances. According to studies, there are some variables that might interact together to cause male factor infertility such as changes in the environment, job, genes, or lifestyle. Oxidative stress-induced damage on sperm DNA, RNA transcripts and telomeres are responsible for male factor infertility. [8] One of the most interesting biomarkers today is pregnancy-associated plasma protein A (PAPP-A), which relates to male infertility and various diseases related to reproduction among men. According to research, it is hypothesized that PAPP-A levels might impact Down evaluation syndrome in ART pregnancies. [9] [7]

It should therefore be understood that though PAPP-A may hold promise as a predictor of reproductive potential, it also has its own constraints and difficulties. A number of factors may explain why some studies identified higher amounts of PAPP-A than others. The mom’s age could also affect the level of PAPP-A. Moreover, adverse obstetric outcomes may be a second reason for these divergences. The study will aid in identifying and examining biomarkers of male infertility [10]. Studies on how biomarker such as PAPP-A could be used to make better assessment of male reproductive functions and ultimately improving success rates of couples who cannot conceive naturally. Such findings indicate that such field of studies will be useful in predicting a male fertility capacity. [11] [12]

PAPP-A is found in the body in a specific structure. It circulates together with proMBP, which is the precursor of eosinophil major basic protein. They form a complex in a 2:2 ratio. Additionally, there is a disulfide bond that weighs 500 kDa. ProMBP plays a role as a proteinase inhibitor, adding to the inhibitory properties of this complex. A minor quantity of unbound PAPP-A, which has a far greater specific activity than the PAPP-A/proMBP complex, is also present in pregnant serum and plasma. One possible explanation for the detectable PAPP-A/proMBP complex activity is a small fraction of partly inhibited PAPP-A that binds to proMBP in a 2:1 ratio.

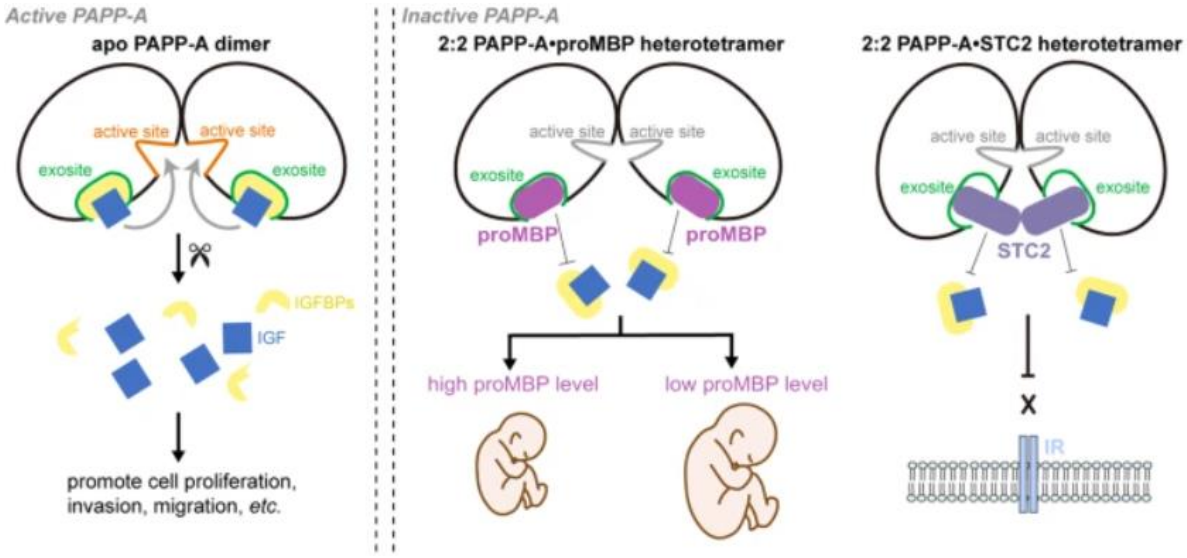

Fig. 1. Structural insights into the covalent regulation of PAPP-A activity by proMBP and STC2[13]

To put it functionally, PAPP-A can cleave IGFBP-2, IGFBP-5, and IGFBP-4. But IGFBP-4 and IGFBP-2 can't act as PAPP-A substrates unless they're coupled to IGFs. Proteolytically active PAPP-[14] A may mainly release IGF-I close to the IGF-I receptor in target tissues, according to certain reports . Research on mice lacking PAPP-A has highlighted its role in keeping circulating IGF-I levels normal even in the face of severe growth retardation. [15]

In clinical settings, elevated levels of circulating PAPP-A have been associated with adverse pregnancy outcomes and cardiovascular risk. Studies suggest that a decreased concentration of PAPP-A leads to adverse events during pregnancy. Consequently, pregnant women may experience preterm delivery of the child, development of pregnancy induced hypertension, or foetal growth restriction among others that may lead to stillbirth. Plasma PAPP-A elevation has been shown to be a predictor of ischemic cardiac events as well as needing revascularisation in ACS patients. [16]

Taken together, these findings suggest that analysing blood PAPP may be used as an indicator of fertility in men. It would be exciting to study some predictive biomarkers for the potential male reproductive ability. The connection between various reproductive diseases and how IGF Signalling regulates reproductive success may be revealed by this study. However, there are some limitations associated with the use of circulating PAPP-A levels in male's fecundity.[8]

2. Role of PAPP-A in Male Fertility

2.1. Potential mechanisms linking PAPP-A to male fertility

One potential indicator of a man's fertility is pregnancy-associated plasma protein-A (PAPP-A), which has been shown to be involved in several biological processes. A metalloproteinase called PAPP-A is produced by a number of organs, including the testes, and it is absolutely necessary for spermatogenesis and fertility. [13] Claiming to release bioactive insulin-like growth factor (IGF) at the IGF receptor upon cleavage of insulin-like growth factor binding proteins (IGFBPs), research has shown that PAPP-A stimulates tissue development. Levels of regulation such as transcriptional control, competing reactions that might block IGFBP-4 from binding, and proteolytic inhibition of PAPP-A all have an impact on this interaction.[15] Additionally, PAPP-A has been associated with tumorigenesis, advancement, and metastasis in breast cancer studies, particularly those focusing on triple-negative breast cancer (TNBC). Tumours with increased protein expression are associated with a higher risk of aggressive malignancies and poor clinical outcomes. The axis of the PAPP-A/IGF was assessed in a group of breast tumours cells, PAPP-A was expressed in 25% of cases. [17]Recent studies summarizing that PAPP-A a role in the deposition of collagen fibres in addition to degradation of IGFBP-5 and plays a role in immune elusion, collectively all these studies climax the role of PAPP-

A in tumour development that extends beyond its effect on IGF-signalling.[18] In addition to its link to cancer, PAPP-A has a role in sperm production and fertility in male mice. In fact, researchers showed that absence of the protein called ATP5D disrupted the spermatogenesis and sperm function in mice knockouts, suggesting that this protein might be a marker or male fertility. [8]
Additionally, studies have shown that PAPP-A blood levels may be indicative of required revascularization and adverse cardiovascular events in people without troponin in persons with ACS. High PAPP-A values appear to be strongly associated with clinical instability and cardiac death in addition to being an independent risk factor for acute myocardial infarction. [19]
The lastly, pointing at a detailed role of PAP-A in few diseases concerning men's health and male fertility. It's function in specific tissue related IGF regulation and sex-promoting role demonstrates possible mechanical tie to male fertility. It is therefore necessary to evaluate PAPP-A levels' association with prognosis of breast cancer, their predictive quality in respect to poor cardiovascular outcomes and their utility as male fertility biomarkers. Therefore, more research is needed in understanding the real clinical significance of PAPP-A as a potential predictive biomarker.[6]

2.2. Existing evidence on the association between PAPP-A levels and male fertility

Various studies have been established that PAPP-A plays a key role in breast cancer but mainly on the aggressive TNBC. Increased PAPP-A expression in pregnancy is evident as a further augmentation of up-regulation in normal tissue compared to neoplasms. Given the fact that PAPP-A up-regulates in aggressive tumour, it could be proposed TNBC as a clinically viable biomarker. Research shows that because PAPP-A affects immune system pathways this is why it can predict fertility. [13]
Other than the role it plays in breast cancer, PAPP-A modifies body development by enhancing IGF-I bioavailability through IGFBP cleavage. Development-oriented normative values have also been studied for new parameters on the GH–IGF axis, including PAPP-A. [12] It has been found that babies at birth have high serum levels of PAPP-A which later decline in concentrations while children grow. It has also been demonstrated that old people tend to have increasing levels of PAPP-A in their blood as they grow old, thus implying that the changing in the level of the PAPP-A that affect the GH-IGH axis would affect the spermatogenesis and so male fertility. [15]
In addition, study has also considered the connection of serum concentrations of PAPP-A with diverse pregnancy results. Research has revealed the relationship between low PAPP-A and several adverse pregnancy outcomes such as preterm delivery, hypertension, foetal growth restriction, and even stillbirth. Including PAPP-A measurements in the monitoring during pregnancy may turn out to be a good predictor of success at the end. [16]Some other research studies have also looked at the increased biomarkers levels of women whose births were by assisted reproductive techniques. In IVF pregnancies, however, -hCG levels could be normal or raised whilst PAPP-A levels in maternal blood are decreased. [1]
There seems to be a link between PAPP-A levels and male infertility as it affects IGF-I bioavailability, pregnancy outcomes, and maternal hormone levels in ART pregnancies. Although much more study is necessary to understand PAPP-A mechanism and predictability, the present results give clues that this may be a marker of male infertility.

3. PAPP-A Levels and Male Reproductive Disorders

3.1. Relationship between PAPP-A levels and sperm quality

The PAPP-A level affect male fertility. It regulates insulin growth factor signalling by cleaving inhibitor IGF binding proteins. This proteolytic process releases free IGF (these have to bind to certain tissue for them to play their biologic role). [13] Based on current information it is clear that PAPP-A should be playing a key role in helping the males to produce high-quality sperm. [20] High levels of PAPP-A have been observed in developing mice where it is expressed higher in organs such as the testes. This strongly suggests that PAPP-A has some role in male fertility and sperm development. There may be some relationship with PAPP-A level and sperm quality affecting future re-evaluation of male subfertility. Also, there is a study that suggested that PAPP-A may be tangled

in the protection of the sperm, within the female reproductive tract, against the localised leucocytosis.[20]

However, more studies should be conducted for better understanding of such relationship and reliance on PAPP-A as male's reproduction marker. These results offer opportunities that enable further investigation into improving PAPP-A as a fertility predictor in men despite current limitations and challenges. [6]

3.2. Association between PAPP-A levels and male infertility

Recent researches show that there are significant connections between men's fertility and PAPP-A levels. Despite the established association between PAPP-A and pregnancy outcomes, its influence on male fertility has generated some controversies. [13]A single research divided PAPP-A levels into three groups: levels of low (less than 0.5 MOM), normal (between 0.5 to 2.5 MOM) and high (more than 2.5 MOM), (MoM: multiple of the median). [21]

83.4 percent of subject showed that PAPP-A levels within the normal range. PAPP-A was found to be in the reference level in 83.4% of the participants. In another study, it was found that mothers who had normal levels of PAPP-A were more likely to deliver at full term compared to mothers whose PAPP-A was above or below the range considered normal. [22]Women whose PAPP-A levels were below 0.5 MOM were much more likely to have miscarriages during their most recent pregnancies. [16]

Other studies have explored the association of high PAPP-A levels with preterm birth as well as complications such as preeclampsia or fetal loss. According to Hughes et al., low level of PAPP-A puts a woman at risk of having fetal growth restriction, severe preeclampsia, or a still born baby. The other researchers found out that SCD, stroke, CV events, infectious deaths, and total mortality were higher among those diabetic patients who underwent haemodialysis. [9]

Based on these findings, elevated PAPP-A levels could be linked to male infertility and harmful pregnancy outcomes. Though these studies illuminate some light on PAPP-A's utility as a biomarker of male fertility and pregnancy outcomes, further investigations need to be conducted in order to grasp out whether the marker performs better than other common fertility biomarkers in anticipating or assess. [6]

However, overall, the current information supports an association of reduced PAPP-A with male infertility and negative gestation outcomes. Nevertheless, we have some concerns regarding PAPPA as a prognostic marker of paternal infertility. Therefore, further studies are required in order to examine whether PAPPA can be considered as a reliable biomarker for screening of male fertility and sensitivity of pregnancies at high or low risk.

4. PAPP-A as a Predictive Biomarker for Fertility

It is possible that the level of circulatory PAPP-A serves as a prognostic biomarker of male fertility, and refers to one of the proteins implicated in diverse reproduction tasks. [15] Research thus far has mainly concentrated on PAPP-A's contribution to female reproduction. Nevertheless, the importance of this biomarker among male should attract more attention and more studies will needed to evaluate it. [23]

4.1. Predictive value of PAPP-A levels in assessing fertility potential

Interestingly, the role of PAPP-A assays for assessing natural fecundity among infertile couples seeking ART also requires scrutiny. It has been established that PAPP-A levels are extremely low during pregnancy, including assisted conceptions like IVF and ICSI. The correlation of such changes with early blood E2 levels and hormonal stimulation or PAPP-A indicates that possibly the PAPP-A could affect hormones level and so have an effect on fertility condition. [13] [24]

The findings suggest the presence of PUFA-derived metabolites like 7(r)-Mar1, 11,12-dhet, 17(s)-hdha, lxa5, pgj2 in the seminal plasma. The chances of infertility were significantly decreased at higher levels of certain metabolites among men with normozoospermia. These results highlight the ability for PUFA derived metabolites to be used as biomarkers for male infertility. [15]

Several interesting findings relate to its role in the IGF pathway. The ability of PAPP-A to clear IGFBPs and stimulate IGF-I bioavailability affects many physiological processes like synthesis of steroids. Based on these findings, PAPP-A influences fertility in the males as well as females through the IGF system. These studies illuminating interrelationship between PAPP-A levels, hormone stimulations, and sperm count. This raises indications of male infertility biomarkers but the role of

PAPP-A levels as a fertility predictor is still elusive. The clinical implications of these observations should also be studied for treatment of male factor infertility.[25]

4.2. Comparison of PAPP-A with other established fertility biomarkers

Within the last decade, men's health professionals have made a considerable effort to seek biomarkers which are predictive for fertility male infertility cases and help doctors give an accurate diagnosis and successful therapy. There is increasing interest in PAPP-A which stimulates the provision of insulin-like growth factor-I and inhibits those IGFBPs by its ability to breakdown. Hence, it is becoming a possible parameter of male fertility marker. It should be compared to other established markers to determine its prospective value and clinical relevance. [13] Several studies have looked at the relationship between PAPP-A serum concentrations and other features of the GH-IGF axis during development. As the concentrations of PAPP-A rose, the free/total IGF-I ratio fell, but the intact/total IGFBP-3 ratio stayed the same. This suggests that PAPP-A changes the quantities of cleaved and uncleaved IGFBPs, which controls the activity of IGF-I. [15][26]

Seminal plasma is also used as another indicator of male infertility. The semen has chemicals that were secreted from the reproductive glands of the males which helps in maintaining healthier sperm cells. Studies show that seminal plasma biomarkers may point out issues like count of semen, movement of semen, shape of semen, and causes of infertility. [27]

Along with being a potential biomarker for male infertility, PAPP-A has some other markers found in seminal plasma. Some of these markers are TEX101, ECM1, and ACRV1. These findings suggest that combining indicators from seminal plasma might yield a better overall assessment of reproduction in men. [28]

In summary, PAPP-A has the potential of becoming a predictive biomarker for male fertility; however, such assessment should consider comparing with current fertility biomarkers. Considering hormone factors and evaluating additional markers in seminal plasma in addition to PAPP-A level may help clinicians understand male fertility better and make appropriate decisions regarding diagnosis and appropriate therapy.

4.3. Limitations and challenges in using PAPP-A as a predictive biomarker

More recently, there has also been a rise of research on markers for identifying problems related to male fertility. As such, strategies are developed to enhance diagnosis and promote effective treatment. It is vital to compare PAPP-A's predictive potential in comparison with its competitor fertility biomarkers. IGF-1's bioavailability increases with degradation of IGFBP binding proteins, such as PAPP-A. In recent years, this protein has attracted increasing attention as a possible male fertility biomarker.[15][13]

A researcher conducted a study on the relationship between the other aspects of the GH-IGF axis and levels of PAPP-A serum concentrations while making development. It was shown that there was a significant association between PAPP-A and free/total IGF-I as well as negative with intact/total IGFBP-3. [21][29]

Therefore, PAPP-A can stimulate or inhibit the activity of IGF-I since it is able to change the level of active (cleaved) and inactive (uncleaved) IGFBPs. [16] Another study considered IVF and ICSI screening for Down Syndrome in the first stage as well. It was observed that blood PAPP-A was significantly lower in pregnancies following IVF/ICSI, compared to normal pregnancies. They established an association between E2 and PAPP-A that may stimulate ovulation in their study. Such findings indicate that hormone related parameters should be taken into account in a consideration of PAPP-A as a predictor of fertility. Controlled ovarian stimulation prior to assisted reproductive procedures such as IVF/ICSI may affect levels of PAPP-A. [8] Biomarkers for male infertility may be present in seminal plasma. This compound contains fundamental elements crucial for normal sperm functions and is generated by male reproductive tissues. Seminal plasma biomarkers may provide some insights into the causes of infertility in a man as well as the number of motile and normal-shaped sperms. [25][30]

Besides PAPP-A other molecular markers detected in seminal fluid, such as TEX101, ECM1 and ACRV1 are considered prospective predictor for diagnosis of male infertility in medical practice. [25] However, the results suggest that there might be further grounds for including a combination of biomarkers that can be obtained from semen plasma into a more holistic evaluation of male fertility potentiality. [28][31]

This notwithstanding, one should consider assessing how PAPP-A stacks up against other well-known fertility biomarkers, irrespective of its seeming potential predictive marker of male fertility. It is necessary that practitioners consider the influence of the hormonal status on diagnosis while studying other indicators in seminal fluid. This will also enable them arrive at well-informed judgments and make appropriate decisions. [13]

5. Conclusion

PAPP-A levels must be compared to other biomarkers to predict fertility. PAPP-A's prognostic biomarker limitations need additional study to completely understand its use. Due to their expanding importance in male infertility, new seminal plasma biomarkers may diagnose and treat male factor infertility. Seminal plasma, released by male reproductive organs, indicates sperm activity and may suggest male infertility. Seminal plasma indicators may enhance male fertility screening and therapy by diagnosing infertile males. Future male factor infertility testing employing seminal plasma biomarkers like PAPP-A may be better understood.

6. References

[1] I. Kirkegaard, N. Uldbjerg, and C. Oxvig, "Biology of pregnancy-associated plasma protein-A in relation to prenatal diagnostics: an overview," Acta Obstet. Gynecol. Scand., vol. 89, no. 9, pp. 1118–1125, 2010.Doi: https://doi.org/10.1016/j.tjog.2015.12.007.

[2] R. Rojas-Rodriguez et al., "PAPPA-mediated adipose tissue remodeling mitigates insulin resistance and protects against gestational diabetes in mice and humans," Sci. Transl. Med., vol. 12, no. 571, p. eaay4145, 2020.Doi:https://doi: 10.1126/scitranslmed. aay4145.

[3] M. T. Overgaard et al., "Complex of pregnancy-associated plasma protein-A and the proform of eosinophil major basic protein: disulfide structure and carbohydrate attachment sites," J. Biol. Chem., vol. 278, no. 4, pp. 2106–2117, 2003. Doi; http://doi.: 10.1074/jbc.M208777200..

[4] V. Barrios et al., "Pregnancy-associated plasma protein (PAPP)-A2 in physiology and disease," Cells, vol. 10, no. 12, p. 3576, 2021.Doi: http://doi: 10.3390/cells10123576.

[5] Y. Yoshimura, "Insulin-like growth factors and their binding proteins: Potential relevance to reproductive physiology," Reprod. Med. Biol., vol. 2, no. 1, pp. 1–24, 2003. Doi: https://doi.org/10.1046%2Fj.1445-5781.2003.00016.x.

[6] Y.-B. Wang et al., "ATP5D is a potential biomarker for male fertility," Oxid. Med. Cell. Longev., vol. 2023, no. 1, p. 4923614, 2023. Doi: http://dx.doi.org/10.1155/2023/4923614.

[7] C. A. Conover and C. Oxvig, "The pregnancy-associated plasma protein-A (PAPP-A) story," Endocr. Rev., vol. 44, no. 6, pp. 1012–1028, 2023. Doi: https://doi.org/10.1210/endrev/bnad017.

[8] C. Heeschen et al., "Pregnancy-associated plasma protein-A levels in patients with acute coronary syndromes: comparison with markers of systemic inflammation, platelet activation, and myocardial necrosis," J. Am. Coll. Cardiol., vol. 45, no. 2, pp. 229–237, 2005. Doi: https://doi.org/10.1016/j.jacc.2004.09.060.

[9] M. Barati, M. Zargar, and B. Asan, "Comparison of First-Trimester Screening Biomarkers in Spontaneous (Natural) and In Vitro Fertilization Pregnancies.," Crescent J. Med. Biol. Sci., vol. 9, no. 2, 2022. Doi: http://dx.doi.org/10.34172/cjmb.2022.19.

[10] N. Kumar and N. K. Singh, "Emerging role of novel seminal plasma bio-markers in Male infertility: a review," Eur. J. Obstet. Gynecol. Reprod. Biol., vol. 253, pp. 170–179, 2020.Doi: https://doi.org/10.1210/endrev/bnad017.

[11] Z. O. Yousif and L. A. Salih, “Study the Level of the Pregnancy Associated Plasma Protein-A (PAPP-A) Isolated from Mature Retrieved Oocyte during ICSI Protocol in Iraqi Infertile women,” Egypt. J. Hosp. Med., vol. 90, no. 1, pp. 1467–1471, 2023. Doi: https://doi.org/10.1016/j.ejogrb.2020.08.015.

[12] B. Wahid, H. Bashir, M. Bilal, K. Wahid, and A. Sumrin, “Developing a deeper insight into reproductive biomarkers,” Clin. Exp. Reprod. Med., vol. 44, no. 4, p. 159, 2017. Doi: https://doi.org/10.21608/ejhm.2023.282370.

[13] C. Oxvig, “The role of PAPP-A in the IGF system: location, location, location,” J. Cell Commun. Signal., vol. 9, pp. 177–187, 2015. Doi: https://doi.org/10.5653%2Fcerm.2017.44.4.159.

[14] C. Oxvig and C. A. Conover, “The Stanniocalcin-PAPP-A-IGFBP-IGF Axis,” J. Clin. Endocrinol. Metab., vol. 108, no. 7, pp. 1624–1633, 2023. Doi: https://doi.org/10.7554%2FeLife.52322.

[15] E. Anckaert, J. Schiettecatte, E. Sleurs, P. Devroey, and J. Smitz, “First trimester screening for Down’s syndrome after assisted reproductive technology: non-male factor infertility is associated with elevated free beta-human chorionic gonadotropin levels at 10–14 weeks of gestation,” Fertil. Steril., vol. 90, no. 4, pp. 1206–1210, 2008. Doi: https://doi.org/10.1210/clinem/dgad053.

[16] M. Movahedi, S. Khanjani, Z. Shahshahan, M. Hajihashemi, F. Farahbod, and E. Shahsavandi, “Evaluation of the relationship between pregnancy-associated plasma protein A (PAPP-A) and pregnancy outcomes,” Adv. Biomed. Res., vol. 12, no. 1, p. 91, 2023.Doi: https://doi.org/10.1016/j.fertnstert.2007.08.050.

[17] P. Prithviraj et al., “Aberrant pregnancy-associated plasma protein-A expression in breast cancers prognosticates clinical outcomes,” Sci. Rep., vol. 10, no. 1, p. 13779, 2020.Doi: https://doi: 10.4103/abr.abr_344_21.

[18] E. C. Jenkins, S. O. Brown, and D. Germain, “The multi-faced role of PAPP-A in post-partum breast cancer: IGF-signaling is only the beginning,” J. Mammary Gland Biol. Neoplasia, vol. 25, pp. 181–189, 2020. Doi: https://doi.org/10.1038/s41598-020-70774-9.

[19] S. L. Harstad and C. A. Conover, “Tissue-specific changes in pregnancy associated plasma protein-A expression with age in mice,” Exp. Gerontol., vol. 57, pp. 13–17, 2014. Doi: https://doi.org/10.1186%2Fs12929-024-01012-x

[20] A. Kumar, T. B. Sridharn, and K. A. Rao, “Role of seminal plasma proteins in effective zygote formation-A success road to pregnancy,” Protein Pept. Lett., vol. 26, no. 4, pp. 238–250, 2019. Doi: https://doi.org/10.1016/j.exger.2014.04.011.

[21] M. Mohrin et al., “Inhibition of longevity regulator PAPP-A modulates tissue homeostasis via restraint of mesenchymal stromal cells,” Aging Cell, vol. 20, no. 3, p. e13313, 2021. Doi: https://doi.org/10.2174/092986652666190208112152.

[22] N. Tarban et al., “Loss of adenosine A3 receptors accelerates skeletal muscle regeneration in mice following cardiotoxin-induced injury,” Cell Death Dis., vol. 14, no. 10, p. 706, 2023. Doi; https://doi.org/10.1111/acel.13313.

[23] R. Hjortebjerg, D. A. Pedersen, J. Mengel-From, L. H. Jørgensen, K. Christensen, and J. Frystyk, “Heritability and circulating concentrations of pregnancy-associated plasma protein-A and stanniocalcin-2 in elderly monozygotic and dizygotic twins,” Front. Endocrinol. (Lausanne)., vol. 14, p. 1193742, 2023. Doi: https://doi.org/10.3389/fendo.2023.1193742.

[24] J. K. Christians, N. Amiri, J. D. Schipilow, S. W. Zhang, and K. I. May-Rashke, “Pappa2 deletion has sex-and age-specific effects on bone in mice,” Growth Horm. IGF Res., vol. 44, pp. 6–10, 2019. Doi: https://doi.org/10.3389/fendo.2023.1193742.

[25] Y. Li, C. Zhou, X. Zhou, L. Song, and R. Hui, "PAPP-A in cardiac and non-cardiac conditions," Clin. Chim. acta, vol. 417, pp. 67–72, 2013. Doi: https://doi.org/10.1016/j.ghir.2018.10.006.
[26] K. Kalantar-Zadeh, T. H. Jafar, D. Nitsch, B. L. Neuen, and V. Perkovic, "Chronic kidney disease," Lancet, vol. 398, no. 10302, pp. 786–802, 2021. Doi: https://doi.org/10.1016/j.cca.2012.12.006.
[27] H. G. Bone et al., "10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension," lancet Diabetes Endocrinol., vol. 5, no. 7, pp. 513–523, 2017. Doi: https://doi.org/10.5114%2Faoms.2020.91283.
[28] L. A. Bach, "40 years of IGF1: IGF-binding proteins," J. Mol. Endocrinol., vol. 61, no. 1, pp. T11–T28, 2018. Doi: http://doi: 10.1016/S2213-8587(17)30138-9.
[29] A. A. Samani, S. Yakar, D. LeRoith, and P. Brodt, "The role of the IGF system in cancer growth and metastasis: overview and recent insights," Endocr. Rev., vol. 28, no. 1, pp. 20–47, 2007. Doi: https://doi.org/10.1530/JME-18-0056.
[30] J. Dereke, C. Nilsson, H. Strevens, M. Landin-Olsson, and M. Hillman, "Pregnancy-associated plasma protein-A2 levels are increased in early-pregnancy gestational diabetes: a novel biomarker for early risk estimation," Diabet. Med., vol. 37, no. 1, pp. 131–137, 2020. Doi: https://doi.org/10.1111/dme.14088.
[31] A. Vashisht and G. K. Gahlay, "Understanding seminal plasma in male infertility: emerging markers and their implications," Andrology, vol. 12, no. 5, pp. 1058–1077, 2024. Doi: https://doi.org/10.1111/andr.13563.

Journal of Basrah Researches (Sciences) **50**(2), 77 (2024)
DOI: https://doi.org/10.56714/bjrs. 50.2.7

تقييم إمكانية تعميم مستوى بروتين البلازما المرتبط بالحمل لدى الرجال كمؤشر حيوي للخصوبة

[1*]زينة سليم زامل، مروة محمود عبدالرحيم[2]، غفران مهدي خليل [3]، شمس خليل ابراهيم[4]

[1]فرع الادوية والسموم ، كلية الصيدلة ، الجامعة المستنصرية، بغداد ، العراق.

[2]علم الأجنة التطبيقي، كلية الطب، جامعة تكريت، تكريت، العراق.

[3] جامعة النهرين كلية الطب قسم التشريح البشري بغداد العراق.

[4]فرع الادوية والسموم ، كلية الصيدلة ، الجامعة المستنصرية، بغداد ، العراق.

معلومات البحث

الاستلام 14 ايار 2024
المراجعة 31 آب 2024
القبول 17 ايلول 2024
النشر 31 كانون الأول 2024

الكلمات المفتاحية

PAPP-A، خصوبة الرجال، جودة الحيوانات المنوية، المؤشرات الحيوية التنبؤية، الاضطرابات الإنجابية.

الملخص

الخلفية كمقياس لخصوبة الرجل، كانت مستويات ف بروتين البلازما المرتبط بالحمل ي الآونة الأخيرة في دائرة الضوء. على الرغم من أن معظم الدراسات ركزت على دورها في مشاكل الحمل مثل انخفاض الوزن عند الولادة وعمر الحمل، إلا أن تأثيرها المحتمل على خصوبة الرجال بدأ يحظى بمزيد من الاهتمام. تهدف إلى تحديد ما إذا كان من الممكن استخدام مستويات بروتين البلازما A المرتبط بالحمل (PAPP-A) في دم الرجال كمؤشر حيوي. هدف الدراسة هو معرفة المزيد عن القوة النذير لهذه المستويات واستخدام التقييم السريري من خلال النظر في العلاقة مع المؤشرات الإنجابية. النتائج على الرغم من عدم وجود أدلة تربط بين بروتين البلازما المرتبط بالحمل وجودة الحيوانات المنوية، إلا أن هناك بعض الأدلة على أن مستويات بروتين البلازما المرتبط بالحمل ترتبط بمشاكل الإنجاب لدى الذكور. يجب أن تنظر الدراسات المستقبلية في إمكانية وجود صلة أقوى بين بروتين البلازما المرتبط بالحمل والعقم عند الرجال. كمؤشر حيوي تنبؤي، فإن بروتين البلازما المرتبط بالحمل لديه عدد من القيود بالمقارنة مع مؤشرات الخصوبة الأخرى الأكثر رسوخًا مثل VAP-1. لتلخيص ذلك، هناك حاجة إلى مزيد من الدراسات لتحديد موثوقية بروتين بروتين البلازما المرتبط بالحمل وقيمته العلاجية، في حين تشير النتائج الأولية إلى وعده كمؤشر حيوي للتنبؤ بخصوبة الذكور. سيكون من الضروري لهذا الجهد فهم المسارات المحتملة التي تربط بروتين البلازما المرتبط بالحمل بخصوبة الرجال. لذلك، من الضروري البحث أكثر في العلاقة بين مستويات بروتين البلازما المرتبط بالحمل والعقم عند الرجال. الاستنتاج: يجب مقارنة مستويات بروتين البلازما المرتبط بالحمل مع المؤشرات الحيوية الأخرى للتنبؤ بخصوبة الرجال.

Citation: Z. S. Zamil et al., J. Basrah Res. (Sci.) **50**(2), 77 (2024).
DOI:https://doi.org/10.56714/bjrs.50.2.7

***Corresponding author email :** zeena90@uomustansiriyah.edu.iq

ISSN: 1817-2695 (Print); 2411-524X (Online)
Online at: https://jou.jobrs.edu.iq