SYSTEMATIC REVIEW

The role of vitamin D supplementation on levator ani muscle remodeling post-delivery

Rahajeng®*, Taufik Ali Zaen®

Department of Obstetrics and Gynecology, Faculty of Medicine, Brawijaya University/ Saiful Anwar General Hospital, Malang, Indonesia.

Article Info

Received Feb 20, 2024 Revised Apr 23, 2024 Accepted May 17, 2024 Published Aug 1, 2024

*Corresponding author:

Rahajeng rahajeng.fk@ub.ac.id

Keywords:

Levator ani Vitamin D supplementation Jackfruit seeds milk Post-delivery Maternal health

ABSTRACT

Objective: Vitamin D is considered a crucial vitamin for the restoration of levator ani muscle strength. Therefore, this study aimed to evaluate the association between vitamin D and levator ani muscle remodeling in the post-delivery period. **Materials and Methods**: The literature search was conducted across three electronic databases, namely PubMed, Google Scholar, and Springerlink. Our investigation yielded a total of 2613 studies, out of which 8 studies were found to meet the inclusion criteria and were subsequently included in our study. Among these, 4 studies specifically examined the impact of vitamin D micronutrient status on the levator ani/pelvic muscles during the post-delivery period.

Results: The mean maximum contraction strength of the levator ani muscles following the administration of vitamin D supplements was 26.77 ± 7.15 cmH2O. The analysis conducted utilizing a paired t-test yielded a p-value of less than 0.05, indicating statistical significance. Additionally, a coefficient correlation of 0.831 was observed, with a p-value also less than 0.05. The findings of this study indicate a noteworthy correlation between levels of vitamin D and the magnitude of levator ani muscle contractions, as evidenced by a statistically significant p-value of less than 0.05.

Conclusion: The administration of vitamin D supplements has been found to play a significant role in the remodeling of the levator ani muscle during the post-delivery period. This is evidenced by the observed increase in strength of the levator ani muscles following vitamin D supplementation.

Copyright: © 2024 Majalah Obstetri & Ginekologi. pISSN:0854-0381 eISSN:2598-1013 This is an open-access article distributed under the terms of the Creative Commons Attribution License as stated in https://creativecommons.org/licenses/by-nc-sa/4.0/deed.id



How to cite: Rahajeng, Zaen TA. The role of vitamin D supplementation on levator ani muscle remodeling post-delivery. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2024;32(2):97-105. doi: 10.20473/mog.V32I22024.97-105.

Highlights:

- 1. In pregnant women, vitamin D insufficiency may play a role in the development of post-delivery illness.
- 2. Vitamin D supplementation is significant in remodeling of post-delivery levator ani muscle.



INTRODUCTION

The levator ani muscle is made up of additional smooth muscle fibers as well as striated muscle fibers. It has a cone shape and is very complex. The levator ani muscle is located on both sides of the lower pelvis and is very important for supporting and elevating the pelvic floor. This makes it easier for other pelvic structures to move. Because it works with the coccygeus muscle, the levator ani muscle is an important part of the pelvic floor muscles. The puborectalis, the pubococcygeus, and the iliococcygeus are the three separate muscles that make up this muscle. There are nerves that connect to most of these muscles that come from the inferior hypogastric plexus, the levator ani muscles, and the pudendal nerves.

According to Timoh et al.,² birth-related levator ani injuries seen on magnetic resonance images in affected women (Fig. 2) have been linked to a much higher risk of vaginal prolapse and a notable 40% drop in pelvic floor muscle strength. An instrumented speculum is a special tool that is often used to measure the isometric strength of the pelvic floor muscles. This tool can measure the highest voluntary force that is used to close the vaginal opening in the mid-sagittal plane. However, the measurement of the force that the vaginal muscles put out when they were at rest and the increase in the maximum strength of that force did not show a noticeable drop as people got older. This finding is surprising because it is common to see striated muscle lose 30 to 40 percent of its volume as a person ages.

A lot of research has been done on this and found that it explains why isometric muscle strength decreases and axial or appendicular striated muscle strength grows more slowly in healthy older adults. If you hurt your levator ani muscle, your pelvic organs may fall out. Many women have experienced pelvic organ prolapse; a health problem that can make them feel less healthy overall. Pelvic organ prolapse may give rise to aberrations in the digestive system, sexual function, and bladder system, alongside psychological, social, and emotional strain that precipitates symptoms of depression, social withdrawal, and anxiety.

The accurate identification of a medical condition is crucial in order to administer appropriate and efficient therapeutic interventions. Levator ani muscle injuries are commonly misdiagnosed, and the therapeutic interventions typically involve limited vaginal repairs. Insufficient focus may be directed towards the dome, also known as the upper part of the vagina, or the descent of the uterus. $\frac{4.5}{1.5}$

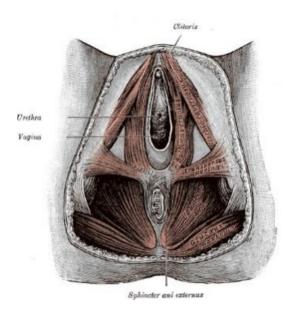
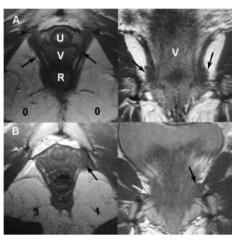


Figure 1. Female perineum, clitoris, urethra, vagina, sphincter ani externus, anus, gluteus maximus, levator ani, transversus perinea.³

There is a pressing necessity for the establishment of nutritional guidelines to prevent levator ani muscle injury. The baseline characteristics encompass the average daily energy and nutrient intakes expressed as a proportion of the recommended dietary allowances among women in the post-delivery period. The study revealed that the post-delivery diet exhibited sufficient intake levels (above 80% of the Recommended Dietary Allowance) for energy (82.6%), protein (80.6%), carbohydrates (99.5%), vitamin C (88.7%), vitamin B2 (95.1%), and vitamin B12 (170.8%). However, inadequate intake levels (below 35%) were observed for vitamin D (12.3%), iron (28.3%), and folate (33.8%).6

People think that vitamin D is very important for many organ systems. It is becoming more common for people to not get enough vitamin D. Several studies have shown that vitamin D deficiency is still common in Indonesia, as well as in Australia and the US. Lower levels of vitamin D in the blood have been linked to a loss of both tone and strength in skeletal muscles in previous research publications. Between 3 and 8 days after giving birth, the pelvic floor muscles tend to get weaker, but they get stronger again between 6 and 10 weeks after giving birth. Most people think that not getting enough vitamin D can cause both skeletal muscle mass and strength to decrease show that when 1,25(OH)2 D3 interacts with the vitamin D receptor (VDR), it starts the process of transcribing proteins that help the body use calcium.





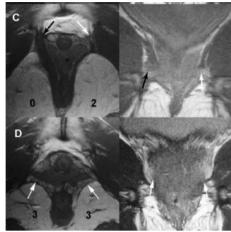


Figure 2. On axial and coronal magnetic resonance images, these examples show the different levels of damage to the levator ani pubovisceral muscle. A: A woman whose muscles are normal; B and D: Three women who each have a major disability; and C: Three women who each have a minor disability. The scores for each side are shown by the handicap scores on the left. There are black arrows that show where the muscle should be and white arrows that show where the muscle is damaged or should be. U stands for the urethra, V for the vaginal canal, and R for the rectum.

It has been shown that vitamin D can affect how strong and well skeletal muscles work. An important link exists between not getting enough vitamin D and having very weak muscles. The levator ani and coccygeus muscles are skeletal muscles that are an important part of the pelvic floor. Some people think that the amount of vitamin D in your body may have an effect on these muscles. Research has indicated that when consumed in suitable quantities, vitamin D has been observed to enhance the efficiency of skeletal muscle. The assessment of micronutrient requirements for the treatment of post-delivery levator ani muscle injury significant challenge for healthcare poses professionals. Consequently, it is imperative to conduct a comparative analysis to determine the efficacy of different micronutrient interventions in addressing this condition. Therefore, this study aimed to evaluate the association between vitamin D and levator ani muscle remodeling in the post-delivery period.

MATERIALS AND METHODS

Search strategy

There was a search of the literature in three electronic databases: PubMed, Google Scholar, and Springerlink. Our research turned up a total of 2613 studies. Of these, 8 met the predetermined criteria for inclusion and were therefore added to our study. These 8 studies gave

detailed information on 4 studies that looked at the micronutrient status of vitamin D and 4 studies that looked at the micronutrient status of collagen, specifically in the levator ani muscle and pelvic muscles after giving birth. Boolean operators "AND" and "OR" were used along with keywords that are related to the clinical questions to do the search. What was found was shown following the rules set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Article selection

The articles acquired through the search process will once again undergo elimination, this time based on the predetermined criteria for inclusion and exclusion. The search for this article employed specific inclusion criteria, namely the utilization of English/Indonesian language, the inclusion of quasi-experimental and observational studies, the examination of the percentage of micronutrient requirements for levator ani muscle repair, and the utilization of human subjects as research participants. Exclusion criteria encompassed interventional studies, studies lacking meta-analytic data, literature sources characterized by regular publication patterns, as well as data derived from reviews or abstracts. The reported results solely pertain to the standard deviation of score coloring, with no additional information provided. After applying the



Maj Obs Gin, Vol. 32 No. 2 August 2024 p-ISSN: 0854-0381; e-ISSN: 2598-1013

predetermined inclusion and exclusion criteria, a total of 19 articles that were deemed relevant were acquired.

Eligibility criteria

The authors collectively engaged in a systematic process of summarizing and evaluating the available evidence by employing a standardized abstraction form. Prior to commencing the process of abstraction and review, the team will conduct tests on the screening and abstraction forms using a variety of articles. The screening and data collection forms will be subject to revision by the team.

Data synthesis

A quantitative synthesis was not conducted for four reasons. Significant variations exist in the operational definition of the condition under treatment across various studies, accompanied by a scarcity of interventions that span a broad spectrum. The present study aims to conduct a trial replication by employing similar interventions while utilizing distinct primary and secondary outcome measures.

Data Extraction

The data obtained from the identified publications encompassed various aspects, such as the study design and corresponding outcomes, the total number of patients involved, the duration of follow-up during the intervention, details regarding the intervention itself, the effectiveness of the intervention, and any additional comments provided. Tables are employed as a means to present data in a descriptive manner and subject it to analysis.

RESULTS AND DISCUSSION

A total of 2163 studies were identified through our search process. After applying the inclusion criteria, a final selection of 8 studies was included in our study. Figure 1 illustrates the flowchart representing the progression of literature through the grading process for the purpose of this review update.

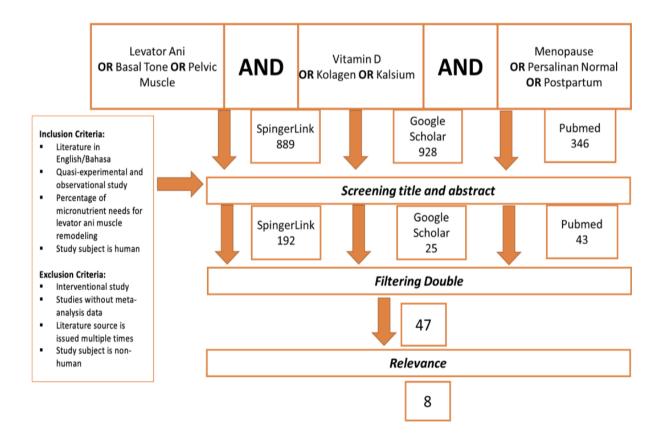


Figure 1. Flowchart of data filtering.



Effects of vitamin D on levator ani muscle remodeling

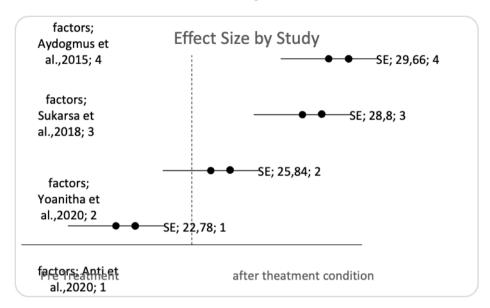


Figure 2. Forest plot effect of vitamin D on levator ani muscle strength.

Research conducted on both animals and humans has demonstrated that Vitamin D3 can enhance muscular strength and function in striated muscle. The clinical manifestation of weakened pelvic floor muscles may manifest as symptoms indicative of pelvic floor dysfunction. There is a notable correlation between the administration of Vitamin D supplementation and muscle, as evidenced by trials conducted by Aydogmus et al.. $\frac{8}{10}$ (SMD = 29.66, 95% CI: 19.36; 39.96) in comparison to Sukarsa et al. $\frac{7}{2}$ (SMD = 22.78, 95% CI: 18.88; 26.68) and Yoanitha et al. 9 (SMD = 25.84 95%) CI: 18.73; 32.95), and The current study examined the average maximum pelvic floor muscle contraction strength after vitamin D3 supplementation. The measured value was 26.77 ± 7.15 cmH2O. The results were statistically significant because the paired t-test pvalue was less than 0.05. They also had a 0.83 correlation coefficient. This suggests a link between vitamin D levels and levator ani muscle strength. Vitamin D levels and levator ani muscle contraction strength are statistically significant at 0.05 or higher. Vitamin D has many effects on striated muscle strength and function. $\frac{7,10}{}$

Research indicates that vitamin D supplementation significantly reduces TGF- β 3 levels. Vitamin D's antioxidant properties may cause this. These properties reduce reactive oxygen species (ROS), which inhibits

MMP. However, Vitamin D increases cell structure-produced type I collagen, elastin, and fibronectin. 11–13 Vitamin D affects striated muscle genomically and nongenomically. Genomically, vitamin D controls gene transcription in striated muscle. By activating vitamin D receptors in muscle nuclear membranes. Muscle cells differentiate and multiply through the insulin growth factor (IGF) pathway after activation, resulting in hypertrophy. When 1,25(OH)D binds to membrane receptors, it has a nongenomic effect. Signal transmission activates the MAPK and PLC pathways. Calcium entry into cell structures is affected by these pathways.

Effect of collagen type I on pelvic muscles

A change (rs1800012) in the gene that codes for type I, alpha 1 collagen at the collagen binding site of Sp1 has been shown to change gene expression and the way transcription factors bind. A small link has been found between minor alleles and lower bone mineral density and a higher risk of breaking a bone in people with osteoporosis. What makes up the vaginal epithelium and endopelvic fascia? They are mostly made up of collagen type I, alpha 1. The gene and protein expression data in pelvic tissue from women with prolapse or stress incontinence who took part in a previous study are very different, showing that the data needs to be improved and refined even more.



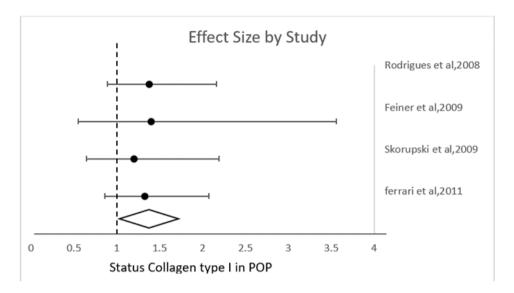


Figure 3. Forest plot status collagen type I in POP

Anatomical POP has been linked to the genetic variant rs1800012 in five different studies. These studies were done in Brazil, Israel, Poland, Italy, and Korea. Because all 30 people who took part in a study had the GG allele, they were not included in the statistical analysis. There was some disagreement between the last four studies, but not a lot. Their effect sizes were still statistically important (OR, 1.33; 95% CI, 1.02-1.73). We think that bias can't be ruled out completely because we don't know much about QC genotypes and the two samples may have been affected by population stratification. One sample is very different from Hardy-Weinberg equilibrium, which suggests a large amount of bias. But leaving out this study would not change the result. It was written by Cartwright et al. 14,15

The study discovered a strong link between vitamin D levels and both the levator ani's basal tone and its maximum contractions. Some of the things that can change a person's vitamin D levels and pelvic floor muscles are their age, body mass index, race, vaginal delivery, diet, and time spent in the sun. Sukarsa et al.⁷ found that women of childbearing age and pregnant women in their first trimester are more likely to have nutritional problems because of the way their bodies work during their periods and during pregnancy. Vitamin D deficiency can be fixed by making more vitamin D, which can be done through fortification, supplements, and other means. A study looked at 25 primiparas and 20 multiparas who had a spontaneous vaginal delivery between 36 and 42 weeks of pregnancy. The results were different for the same women 3-8 days after giving birth, 6-10 weeks after giving birth, and 9-15 months after giving birth. Pain during contractions and/or pressure inside the abdomen

during the exam have both been linked to the chance of perimetric assessments being biased. 16-19 This study shows that taking extra vitamin D is important for remodeling the levator ani muscle after giving birth.

If you don't get enough vitamin D, the calcium balance in your pelvic floor muscles gets off, which makes them less effective and can cause problems with your pelvic floor. A small amount of vitamin D has been shown to improve the function of skeletal muscles. PFMT is meant to make the levator ani muscles stronger, which are very important for a woman's ability to control her bladder. This should be your first line of defense when dealing with SUI, OAB, UUI, or FI. Studies using random assignments have shown that strengthening the muscles in the pelvic floor can help reduce urinary incontinence by 54 to 75%. Low 25(OH)D levels may impair skeletal muscle function, which the urethra needs. The levator ani, extrinsic urethral, and external anal sphincters may work better with normal vitamin D levels. Thus, vitamin D levels may affect how well behavioral therapy helps PFMT women control urinary and fecal incontinence. More research is needed to determine how vitamin D affects the levator ani muscle and how vitamin D supplements and PFMT may treat pelvic floor symptoms.

The study's correlation analysis backs up the explanation that was put forward. Vitamin D and muscle strength have been looked at in a lot of different studies. Aydogmus et al. discovered a link between the strength of the levator ani muscle and the amount of vitamin D a woman had before giving birth. When women had enough vitamin D, their pelvic floor muscles were stronger after giving birth. Low vitamin



Maj Obs Gin, Vol. 32 No. 2 August 2024 p-ISSN: 0854-0381; e-ISSN: 2598-1013

D levels in the third trimester have been linked to pelvic floor muscles that aren't as strong after giving birth. 20-23 A study by Parker et al. looked at 394 women who said they had problems with their pelvic floor and found that not getting enough vitamin D was linked to more urinary incontinence and other colorectal symptoms that made their quality of life worse. In a study of 99 girls ages 12 to 14, Ward et al. found that vitamin D levels were linked to better measures of strength, speed, and vertical jump. Other studies have looked at what happens to muscle tissue when people take extra vitamin D. Teenage girls between the ages of 12 and 14 who took 150,000 IU of vitamin D supplements every three months for a year showed improvements in their strength, height, and efficiency when jumping, according to a study by Ward et al. 24-26

Gabriel et al. did an in vitro study and found that the sacrouterine ligament in the neck may be able to hold up to 17 kg of weight before the hip gives way. The ECM is made up of elastin, collagen, and fibronectin. It is the main structure-supporting protein. 4,27 There is a special structure to the ligaments of a woman's genitalia because elastin and collagen can change shape during the reproductive stages of her life. The component goes back to its pre-pregnancy levels after giving birth, even though it rose a lot during pregnancy. POP is more likely in older women, multi-pregnant women, and vaginal birthers. Oxford Family Planning found that POP hospital admissions increased four times for women with one child, eight times for two children, and ten times for more than two children in a prospective study of 17,000 women.

New studies show that vitamin D deficiency increases POP risk. Vitamin D supports skin and heart connective tissues better than bone building and mineral density. Here, Skowronska et al. 10,19,28 explain the biomolecular processes that regulate vitamin D intake or exposure in POP. TGF-3 levels dropped significantly after vitamin D exposure. Due to its antioxidant properties, vitamin D reduces ROS and matrix metalloproteinase. Vitamin D boosts type I collagen, elastin, and fibronectin production. Grinnell also found that vitamin D grows fibroblast growth factor II, which makes elastin and collagen. Vitamin D makes it easier for skin and heart tissues to make collagen types I and II. Along with the transcription process, this way of copying is thought to be passed down from parent to child. 11,26-29

Strength and limitation of the study

Strength of this study are there is specific micronutrient and specific vitamin D observed on this study. The limitation of this study is that there is wide gap of age of

post-partum woman observed and there isn't exact measurement of levator ani muscle strength.

CONCLUSION

During pregnancy and childbirth, the levator ani muscles are under a lot of stress from both mechanical and neurological issues. However, there are other issues that come into play as well. Women who are pregnant and don't get enough vitamin D may have more problems after giving birth. Strength gains in the levator ani muscle after taking vitamin D3 supplements after giving birth show that vitamin D is an important part of muscle remodeling after giving birth.

DISCLOSURES

Acknowledgment

The authors would like to express a humble gratitude to Faculty of Medicine, Universitas Brawijaya, for the profound support in the accomplishment of this paper.

Conflict of interest

There is no conflict of interest to disclose.

Funding

There is no financial conflict of interest to disclose.

Author contribution

All of the authors worked on this study in some way, including planning, collecting and analysing data, writing, and getting permission to publish.

REFERENCES

- 1. Němec M, Horčička L, Dibonová M, et al. Analýza stavu muskulo-fasciální složky pánevního dna pomocí MRI u pacientek před plánovaným vaginálním rekonstrukčním výkonem pro symptomatický sestup pánevního dna [MRI analysis of the musculo-fascial component of pelvic woman before planned reconstruction procedur for symptomatic pelvic prolapse]. Ceska Gynekol. 2018 Summer;83(2):84-93. Czech. PMID: 29869505.
- Nyangoh Timoh K, Bessede T, Zaitouna M, et al. Anatomie du muscle élévateur de l'anus et applications en gynécologie obstétrique [Anatomy of the levator ani muscle and implications for



- obstetrics and gynaecology]. Gynécologie Obstétrique & Fertilité. 2015;43(1):84-90. doi: 10.1016/j.gyobfe.2014.11.015.
- Gowda SN, Bordoni B. Anatomy, Abdomen and Pelvis: Levator Ani Muscle. 2022 Oct 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. <u>PMID</u>: 32310538.
- Rahajeng R. The increased of MMP-9 and MMP-2 with the decreased of TIMP-1 on the uterosacral ligament after childbirth. Pan Afr Med J. 2018;30: 283. doi: 10.11604/pamj.2018.30.283.9905. PMID: 30637068; PMCID: PMC6317396.
- Abbas N, Reid F. Pelvic organ prolapse: anatomical and functional assessment. Obstet Gynaecol Reprod Med. 2022;32(7):127–34. doi: 10.1016/j.ogrm. 2022.04.006.
- Aparicio E, Jardí C, Bedmar C, et al. Nutrient intake during pregnancy and post-partum: ECLIPSES Study. Nutrients. 2020;12(5):1325. doi: 10.3390/nu12051325. PMID: 32392706; PMCID: PMC7285175.
- Sukarsa RA, Anti DN, Purwara BH, et al. Effect of vitamin D3 supplementation on levator ani muscle strength in primipara pregnancy with postpartum vitamin D3 deficiency. Indonesian Journal of Obstetrics and Gynecology. 2020;8(4):231–6. doi: 10.32771/inajog.v8i4.1063.
- Aydogmus S, Kelekci S, Aydogmus H, et al. Association of antepartum vitamin D levels with postpartum pelvic floor muscle strength and symptoms. Int Urogynecol J. 2015;26(8):1179-84. doi: 10.1007/s00192-015-2671-3. Epub 2015 Mar 20. PMID: 25792352.
- Yoanitha N, Purwara BH, Ruslina I, et al. The effect of vitamin D3 supplementation on increases of levator ani contraction strength in women with uterine prolapse. Indonesian Journal of Obstetrics and Gynecology. 2020;8(3):174-8. doi: 10.32771/ inajog.v8i3.1184.
- Mangir N, Hillary CJ, Chapple CR, et al. Oestradiol-releasing biodegradable mesh stimulates collagen production and angiogenesis: An approach to improving biomaterial integration in pelvic floor repair. Eur Urol Focus. 2019;5(2):280-9. doi: 10. 1016/j.euf.2017.05.004. Epub 2017 Jun 3. PMID: 28753895.
- 11. Roman S, Mangir N, Bissoli J, et al. Biodegradable scaffolds designed to mimic fascia-like properties for the treatment of pelvic organ prolapse and stress urinary incontinence. J Biomater Appl. 2016;30(10):1578-88. doi: 10.1177/0885328216633373. Epub 2016 Feb 18. PMID: 26896234.
- 12. Mangir N, Bullock AJ, Roman S, et al. Production of ascorbic acid releasing biomaterials for pelvic floor repair. Acta Biomater. 2016;29:188-97. doi:

- <u>10.1016/j.actbio.2015.10.019</u>. Epub 2015 Oct 19. PMID: 26478470; PMCID: PMC4678952.
- Cartwright R, Kirby AC, Tikkinen KA, et al. Systematic review and metaanalysis of genetic association studies of urinary symptoms and prolapse in women. Am J Obstet Gynecol. 2015; 212(2):199.e1-24. doi: 10.1016/j.ajog.2014.08.005. Epub 2014 Aug 8. PMID: 25111588; PMCID: PMC4342521.
- Da Silva AS, Asfour V, Digesu GA, et al. Levator Ani avulsion: The histological composition of this site. A cadaveric study. Neurourol Urodyn. 2019; 38(1):123-9. doi: 10.1002/nau.23847. Epub 2018 Oct 30. PMID: 30375038.
- 15. Ali ML, Kumar SP, Bjornstad K, et al. The sheep as an animal model for heart valve research. Cardiovasc Surg. 1996;4(4):543-9. doi: 10.1016/0967-2109(95)00142-5. PMID: 8866098...
- 16. Scaramuzzi RJ, Campbell BK, Downing JA, et al. A review of the effects of supplementary nutrition in the ewe on the concentrations of reproductive and metabolic hormones and the mechanisms that regulate folliculogenesis and ovulation rate. Reprod Nutr Dev. 2006;46(4):339-54. doi: 10.1051/rnd: 2006016. Epub 2006 Jul 7. PMID: 16824444.
- 17. Kurniadi A, Dewi AK, Sasotya RMS, et al. Effect of Vitamin D analog supplementation on levator ani strength and plasma Vitamin D receptor expression in uterine prolapse patients. Sci Rep. 2023;13(1):3616. doi: 10.1038/s41598-023-30842-2. PMID: 36869168; PMCID: PMC9984360.
- Rezaei H, Asefnejad A, Daliri-Joupari M, et al. Invitro cellular and in-vivo investigation of ascorbic acid and β-glycerophosphate loaded gelatin/sodium alginate injectable hydrogels for urinary incontinence treatment. Prog Biomater. 2021;10(2):161-71. doi: 10.1007/s40204-021-00160-9. Epub 2021 Jun 24. PMID: 34169484; PMCID: PMC 8271082.
- 19. Schimpf M, Tulikangas P. Evolution of the female pelvis and relationships to pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16(4):315-20. doi: 10.1007/s00192-004-1258-1. Epub 2005 Jan 15. PMID: 15654501.
- 20. Hogervorst T, Bouma HW, de Vos J. Evolution of the hip and pelvis. Acta Orthop Suppl. 2009;80(336):1-39. doi: 10.1080/17453690610046620. PMID: 19919389.
- 21. Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. Lancet. 2007;369(9566):1027-38. doi: 10. 1016/S0140-6736(07)60462-0. PMID: 17382829.
- 22. Guler Z, Roovers JP. Role of fibroblasts and myofibroblasts on the pathogenesis and treatment of pelvic organ prolapse. Biomolecules. 2022;12(1):94. doi: 10.3390/biom12010094. PMID: 3505 3242; PMCID: PMC8773530.



- 23. Ben Menachem-Zidon O, Gropp M, Reubinoff B, et al. Mesenchymal stem cell transplantation improves biomechanical properties of vaginal tissue following full-thickness incision in aged rats. Stem Cell Reports. 2022;17(11):2565-78. doi: 10.1016/j.stemcr.2022.09.005. Epub 2022 Oct 13. PMID: 36240774; PMCID: PMC9669396.
- 24. Sundrani D, Narang A, Mehendale S, et al. Investigating the expression of MMPs and TIMPs in preterm placenta and role of CpG methylation in regulating MMP-9 expression. IUBMB Life. 2017;69(12):985-93. doi: 10.1002/iub.1687. Epub 2017 Nov 11. PMID: 29130646.
- Wieslander CK, Rahn DD, McIntire DD, et al. Quantification of pelvic organ prolapse in mice: vaginal protease activity precedes increased MOPQ scores in fibulin 5 knockout mice. Biol Reprod. 2009;80(3):407-14. doi: 10.1095/biolreprod.108. 072900. Epub 2008 Nov 5. PMID: 18987327; PMCID: PMC2805390.
- 26. Barat S, Bouzari Z, Mehdinia S, et al. The serum level of Vitamin D in women with urinary

- incontinence due to pelvic floor disorder and prolapse: a regional case-control study on Iranian population. International Journal of Women's Health and Reproduction Sciences. 2015;3(3):126-31. doi: 10.15296/ijwhr.2019.11.
- 27. Wang HL, Zhou C, Zhang YZ. [Role of matrix metalloproteinase-2,9 and their inhibitors in premature rupture of membranes]. Zhonghua Fu Chan Ke Za Zhi. 2005;40(1):29-33. Chinese. PMID: 15774089.
- 28. Maymon E, Romero R, Pacora P, et al. A role for the 72 kDa gelatinase (MMP-2) and its inhibitor (TIMP-2) in human parturition, premature rupture of membranes and intraamniotic infection. J Perinat Med. 2001;29(4):308-16. doi: 10.1515/JPM.2001. 044. PMID: 11565199.
- 29. Strinic T, Vulic M, Tomic S, et al. Matrix metalloproteinases-1, -2 expression in uterosacral ligaments from women with pelvic organ prolapse. Maturitas. 2009;64(2):132-5. doi: 10.1016/j. maturitas.2009.08.008. Epub 2009 Sep 17. PMID: 19765922.

