



## RESEARCH ARTICLE

## The Role of Transforming Growth Factor Beta (TGF- $\beta$ ) in Pelvic Organ Prolapse : A Systematic Review

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### Abstract

**Introduction:** Pelvic organ prolapse (POP) is a gynaecological disorder with a rising prevalence, significantly affecting quality of life. While the pathogenesis of POP is multifactorial, alterations in the extracellular matrix (ECM) have been implicated, particularly the role of transforming growth factor-beta (TGF- $\beta$ ) in ECM remodelling. However, the precise relationship between TGF- $\beta$  and POP remains unclear.

**Methods:** A systematic review was conducted following PRISMA guidelines. Relevant studies were identified from PubMed, Scopus, Web of Science, and the Cochrane Library. Inclusion criteria focused on studies investigating TGF- $\beta$  expression in women with POP. Data extraction included study design, patient demographics, TGF- $\beta$  detection methods, and key findings.

**Results:** Analysis of nine studies revealed mixed findings. Four studies reported a significant reduction in TGF- $\beta$ 1 expression in POP patients, suggesting impaired ECM regulation via the TGF- $\beta$ 1/Smad3 pathway. Three studies found no significant differences in TGF- $\beta$  levels between POP and control groups, while one study linked increased TGF- $\beta$ 1 levels to severe prolapse, possibly as a compensatory response. Variations in methodology, sample size, and patient characteristics contributed to inconsistencies across studies.

**Conclusion:** Current evidence suggests that TGF- $\beta$ 1 plays a role in POP pathogenesis, with lower levels potentially weakening ECM integrity and higher levels in advanced cases reflecting a failed reparative response. Further research is needed to explore TGF- $\beta$  interactions with other biomarkers and assess its potential as a therapeutic target.

**Keywords:** Pelvic organ prolapse, transforming growth factor-beta, extracellular matrix, TGF- $\beta$ 1, ECM remodelling, systematic review

## INTRODUCTION

Pelvic organ prolapse (POP) is clinically defined as the downward descent of the anterior or posterior vaginal wall, the uterus, or the vaginal vault into or through the vagina.<sup>1,2</sup> The pelvic organs are the uterus and/or different vaginal compartments and the surrounding organs such as the bladder, rectum and bowel. Pelvic organ prolapse is the descent of one or more vaginal compartments (anterior and posterior), the uterus (cervix), or the apex of the vagina (vaginal stump after hysterectomy).<sup>3</sup> It is a common gynecological condition, detected in 30–76% of women during routine examinations, even when no specific symptoms are reported. POP can negatively affect sexual function, body image, and overall quality of life. According to a study by Wu et al., the prevalence of POP is projected to rise by 46%, reaching an estimated 4.9 million cases by 2050.<sup>4</sup> Pelvic organ prolapse is the most common condition in elder women and the incidence reached 26.4% in tertiary hospital in Indonesia.<sup>5</sup> The increasing incidence of POP, particularly with aging, imposes substantial healthcare costs and financial strain on medical systems.<sup>1</sup>

Pelvic organ prolapse (POP) is a multifactorial condition with unclear pathophysiology, influenced by factors such as aging, menopause, parity, and increased intra-abdominal pressure. A combination of anatomical, physiological, genetic, lifestyle, and reproductive factors interact throughout a woman's lifetime to contribute to pelvic floor dysfunction. Many studies have linked parity to a higher incidence of pelvic organ prolapse. There is a strong association between pregnancy and vaginal delivery, which causes direct injury to the muscles and connective tissue of the pelvic floor. Normally, the vagina is horizontal over the levator ani muscles. Pelvic floor damage causes the levator ani muscles to become more vertical, opening the vagina and disrupting the connective tissue support mechanism. Through biomechanical modeling, it has been suggested that the second stage of labor causes the levator ani muscles to stretch more than 200% beyond the threshold of injury.<sup>5</sup>

The most common symptom is a protrusion through the vagina. During the annual well-woman visit, it is important to screen women for urinary symptoms and protrusions, which are often embarrassing for a woman to report at her annual visit. A physical examination is essential to diagnose and categorize the type of prolapse. Examination findings will vary depending on the fullness of the bladder and rectum. Women who present with procidentia (third compartment prolapse) may complain of vaginal discharge due to vaginal friction or erosion of the vaginal epithelium. Patients with pelvic organ prolapse tend to have other pelvic floor dysfunctions. Up to 40% will have urinary incontinence, 37% will have an overactive bladder, and 50% will have fecal incontinence. In the majority of cases, pelvic organ prolapse can mask urinary incontinence.<sup>5</sup>

Structural defects in pelvic support and abnormalities in connective tissue may contribute to its development. The uterosacral ligament (USL) plays a key role in pelvic stability, with extracellular matrix (ECM) components like collagen and elastin being implicated in POP.<sup>2</sup> In pelvic organ prolapse, there is a pelvic floor defect caused by the vulnerability of the supporting structures due to various factors and leads to the descent and displacement of the pelvic organs, resulting in anatomical location anomalies and pelvic floor dysfunction. Pelvic organ support is provided by the

levator ani muscles, pelvic fascia, and ligaments. The supportive effect of these structures depends not only on the quantity of their cellular components but also on their quality.<sup>3</sup> Damage to the extracellular matrix results in changes in the strength of the pelvic floor supporting structures and leads to pelvic organ prolapse.<sup>6</sup>

Peter Petros introduced the integral theory as the basis for the development of pelvic organ prolapse. The integral theory aims to determine the location and identify the damaged pelvic floor ligaments or fascia. The diagnostic system based on this integral theory uses a 3-zone approach to describe the complexity of symptoms. Based on this theory, pelvic organ prolapse occurs due to over laxity of the vaginal connective tissue and its supporting ligaments.<sup>7</sup> While De Lancey stated that the connective tissue, pelvic floor fascia, and pelvic floor ligaments are responsible for holding the pelvic organs in their normal position and each injury at each level causes damage to a specific area. De Lancey's theory can determine the diagnosis and treatment according to the level of damage. The pelvic floor connective tissue connects the vagina and lateral uterus to the pelvic side walls. The connective tissue is divided into three levels.<sup>8</sup>

Transforming growth factor-beta 1 (TGF- $\beta$ 1) is a cytokine involved in extracellular matrix remodelling and has been linked to conditions involving weakened fascial support, including inguinal hernias. Main sources of TGF- $\beta$  are bone and platelets. TGF- $\beta$  is a polypeptide that has a direct stimulatory effect on collagen synthesis. TGF- $\beta$  activates fibroblasts to induce collagen formation, endothelial cells for angiogenesis, and mesenchymal cells to enhance wound healing.<sup>9</sup>

TGF- $\beta$  consists of 3 isoforms, namely TGF- $\beta$ 1, - $\beta$ 2, - $\beta$ 3 which have overlapping functions with each other in the wound healing process. TGF- $\beta$ 1 increases the angiogenesis process. TGF- $\beta$ 2 and TGF- $\beta$ 3 are associated with scar tissue formation and fibrosis. Both increase fibroblast and myofibroblast differentiation, extracellular matrix deposition, wound contraction and scar tissue formation. TGF- $\beta$  stimulates the proliferation of undifferentiated MSCs, regulates endothelial, fibroblast and osteoblast mitogenesis. In addition, it inhibits macrophage and lymphocyte proliferation and metalloproteinase activity. TGF- $\beta$  regulates collagen synthesis and collagenase secretion.<sup>8</sup>

GF-1 has two important functions: chemotaxis of vascular endothelial cells into the wound resulting in angiogenesis and promoting differentiation of several cell lines including chondroblasts, myoblasts, osteoblasts, and hematopoietic cells. TGF- $\beta$  is a recently discovered family of proteins. The two major sources of this protein are platelets and macrophages. TGF- $\beta$  causes chemotactic attraction and activation of monocytes, macrophages, and fibroblasts. Activated fibroblasts increase extracellular matrix and collagen formation and also stimulate the cells' ability to contract the provisional wound matrix. Macrophage infiltration promotes TGF- $\beta$  which induces extracellular matrix such as collagen and fibronectin; however alpha-mangostin prevents the increase of these molecules in rats with Cisplatin-induced nephrotoxicity. TGF- $\beta$  released from platelet alpha granules is a mitogen for fibroblasts, smooth muscle cells, and osteoblasts. In addition, TGF- $\beta$  also promotes angiogenesis and extracellular matrix production.<sup>7</sup>

Altered TGF- $\beta$ 1 expression has been observed in pelvic organ prolapse, but its exact role and

prognostic significance remain unclear.<sup>11,12</sup> Decreased expression of TGF- $\beta$ 1 in pelvic organ prolapse has been shown in pelvic organ prolapse tissue. Sugaya K, et al report that Plasma TGF- $\beta$ 1 levels were significantly lower in patients than in healthy controls. POP-Q stage was not significantly different between the uterine prolapse and cystocele subgroups, but POP-Q stage IV was diagnosed in 63% of patients with uterine prolapse and 7% of those with cystocele. Plasma TGF- $\beta$ 1 levels were significantly lower in the cystocele subgroup than in the uterine prolapse subgroup.<sup>13</sup>

Recent studies on POP have focused on the abnormal structure and organization of pelvic floor connective tissue and the molecular alterations in uterosacral ligaments. The breakdown of the extracellular matrix decreases the strength of supportive structures and lead to pelvic organ prolapse. Transforming growth factor-beta 1 cytokine expression decrease in fibroblast, pubovaginal fascia dan cardinale ligament tissue. Transforming growth factor-beta 1 regulate multiple enzymes and extracellular matrix components. Collagen expression was positively correlated with level of TGF- $\beta$ 1 expression level. TGF- $\beta$ 1 involved in the synthesis of the extracellular matrix and the inhibition of matrix metalloproteinases. Molecular mechanism of TGF- $\beta$ 1 remains elusive, TGF- $\beta$ 1 is increase in conditions with increased fibrosis tissue.<sup>13</sup>

Kong M et al revealed that the protein expression levels of integrin- $\beta$ 1, TGF- $\beta$ 1 and TIMP-1 were significantly reduced, and the protein expression levels of MMP-1 were significantly increased in tissues from patients with PoP compared with in tissues from the control group.<sup>14</sup>

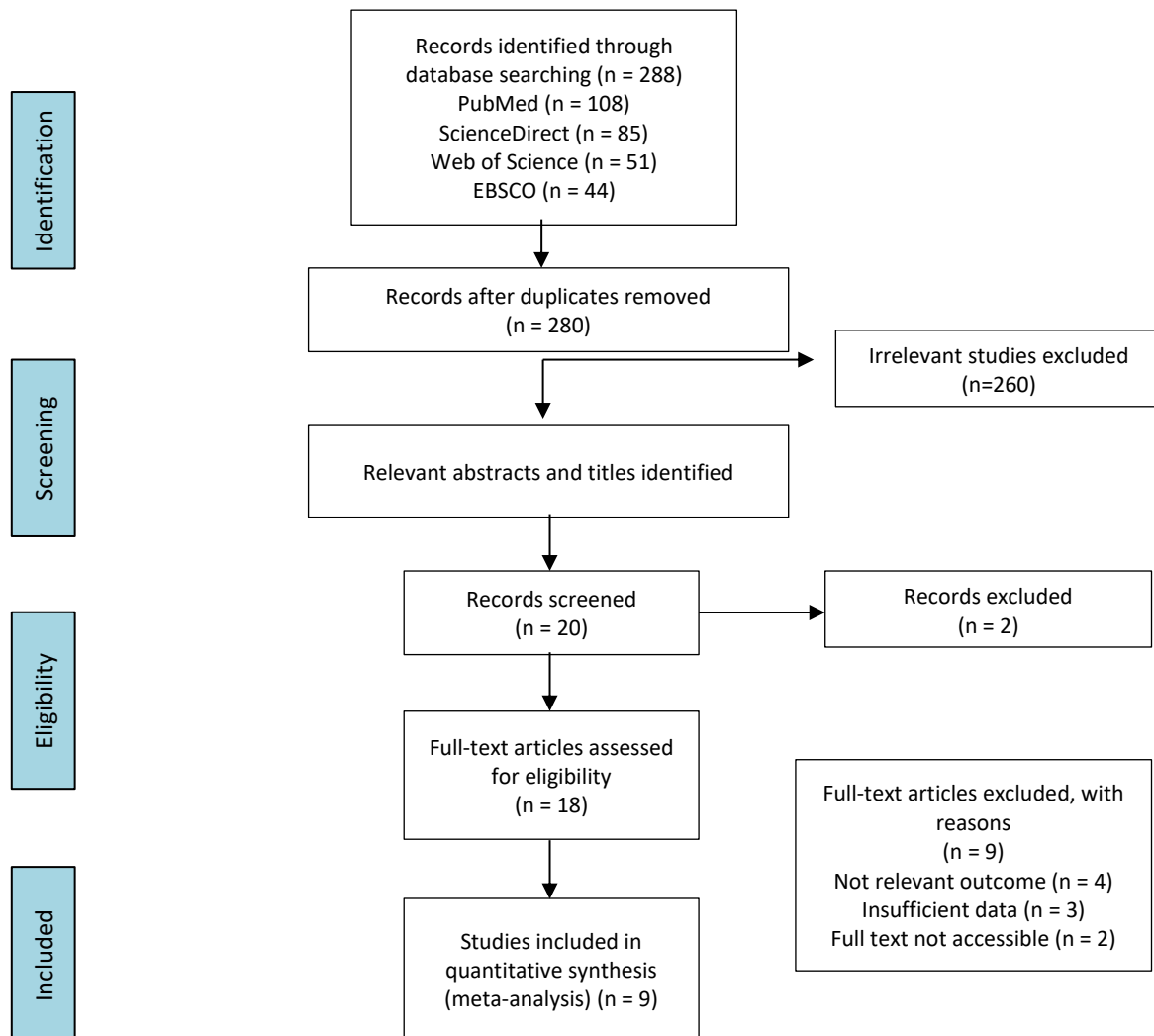
This systematic review aims to summarize the existing literature on the association between TGF- $\beta$  and POP, with a focus on its potential as a biomarker and therapeutic target.

## METHODS

The PRISMA methodology is used for this systematic review. The research question follows the PICO framework, with the population being women with *Pelvic Organ Prolapse (POP)*, the intervention/exposure focusing on *TGF- $\beta$* , comparisons involving normal tissues or other influencing factors, and outcomes assessing *TGF- $\beta$ 's* role in *POP* pathogenesis, progression, or treatment. A systematic literature search will be conducted across PubMed, ScienceDirect, Web of Science, and the Cochrane Library.

Following PRISMA guidelines, the selection process includes duplicate removal, title and abstract screening, and full-text assessment based on inclusion and exclusion criteria. Eligible studies will focus on the *TGF- $\beta$ -POP* relationship, while irrelevant studies, non-English papers, conference abstracts, and inaccessible full texts will be excluded.

Key data extracted will include patient demographics, *TGF-β* analysis methods (e.g., immunohistochemistry, ELISA, PCR), and primary findings. A narrative synthesis will be conducted for heterogeneous studies, while a meta-analysis may be performed if data pooling is feasible. The final report will align with PRISMA guidelines, incorporating a selection flowchart, summary tables, and a discussion on clinical implications and limitations.



**Fig. 1** Flow diagram of the research procedure

## RESULT

Based on an analysis of nine studies, the relationship between transforming growth factor- $\beta$  (TGF- $\beta$ ), particularly the TGF- $\beta$ 1 isoform, and pelvic organ prolapse (POP) shows mixed results, although several trends emerge.

Four studies (Ying Zhao et al., 2021; Xiao-Ying Qi et al., 2011; Mellie Nur Akin et al., 2021; Cheng Liu et al., 2017) reported a significant reduction in TGF- $\beta$ 1 expression in patients with POP compared to controls ( $p < 0.05$ ).<sup>15-18</sup> Notably, Cheng Liu et al. (2017) associated this decrease with disruptions in extracellular matrix (ECM) regulation, specifically a reduction in collagen, elastin, and

TIMP-2, accompanied by an increase in MMP-2/9.<sup>18</sup> This suggests a possible mechanism via the TGF- $\beta$ 1/Smad3 pathway. Further genetic (Mellie Nur Akin et al., 2021)<sup>17</sup> and molecular (Liping Zhang et al., 2020)<sup>6</sup> studies support the role of TGF- $\beta$ 1 in POP pathogenesis by highlighting its interactions with genes like HOXA11 and its regulatory influence on ECM remodelling.

On the other hand, three studies (Antonella Vetusch et al.<sup>19</sup>, 2018; Weiwei Ying et al.<sup>20</sup>, 2022; Ava Leegant et al., 2015)<sup>21</sup> did not find significant differences in TGF- $\beta$  expression between POP patients and control groups. However, Weiwei Ying et al. (2022) observed increased levels of MMP-2/9 and decreased levels of CD44, suggesting that other biomarkers might also play an important role.<sup>20</sup>

One study (Greta Lisa Carlin et al., 2020)<sup>22</sup> found that although overall TGF- $\beta$ 1 levels did not differ significantly between POP and control groups, TGF- $\beta$ 1 levels were higher in cases of severe prolapse. This finding indicates that TGF- $\beta$ 1 may be more closely related to disease progression rather than the initial onset of POP.

**Table 1.** Analysis Of Nine Studies

| No | Author (Year)                    | Study Design                       | Population                                       | TGF- $\beta$ Analysis Method       | Main Findings                                                                          | Conclusion                                                         |
|----|----------------------------------|------------------------------------|--------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| 1  | Ying Zhao et al. (2021)          | Observational, laboratory analysis | 30 POP patients, 30 controls                     | Immunohistochemistry, Western blot | TGF- $\beta$ 1 were significantly lower in POP patients (p<0.05).                      | Reduced TGF- $\beta$ 1 may be associated with POP occurrence       |
| 2  | Antone lla Vetusch et al. (2018) | Observational                      | 20 POP patients ( $\geq$ stage III), 10 controls | Immunohistochemistry               | No significant difference in TGF- $\beta$ expression between POP patients and controls | No significant association between TGF- $\beta$ expression and POP |
| 3  | Xiao-Ying Qi et al. (2011)       | Observational, laboratory analysis | 50 POP patients, 20 controls                     | Immunohistochemistry, Western blot | TGF- $\beta$ 1 was significantly lower in POP patients compared to controls (p<0.05)   | TGF- $\beta$ 1 play a role in POP pathogenesis                     |
| 4  | Melike Nur Akin et al. (2021)    | Observational, genetic analysis    | 10 POP+UUI patients, 14 controls                 | qPCR, ELISA                        | TGF- $\beta$ 1 was significantly decreased in POP (p=0.006)                            | Reduced TGF- $\beta$ 1 may contribute to POP pathogenesis          |
| 5  | Cheng Liu et al.                 | Case-control, in vitro study       | 60 women undergoing hysterectomy                 | Masson's trichrome staining,       | Decreased TGF- $\beta$ 1, collagen, elastin, and TIMP-2 in POP group;                  | TGF- $\beta$ 1 may predict POP severity and                        |

| No | Author (Year)                    | Study Design                  | Population                                                                          | TGF- $\beta$ Analysis Method                        | Main Findings                                                                                                          | Conclusion                                                                           |
|----|----------------------------------|-------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
|    | al. (2017)                       |                               | y (30 with POP grade II-IV, 30 controls)                                            | Immunohistochemistry, RT-qPCR                       | increased MMP-2/9. In vitro, TGF- $\beta$ 1 protected ECM through TGF- $\beta$ 1/Smad3 pathway.                        | serve as a therapeutic target.                                                       |
| 6  | Weiwei Ying et al. (2022)        | Matched case-control          | 60 postmenopausal women (30 with POP stage $\geq 2$ , 30 controls)                  | Immunohistochemistry, ImageJ quantification         | TGF- $\beta$ expression was similar in both groups; MMP-2/9 increased in POP; CD44 decreased.                          | CD44, MMP-2, and MMP-9 may be biomarkers for POP progression.                        |
| 7  | Liping Zhang et al. (2020)       | Case-control, molecular study | USL samples from POP patients and controls                                          | Immunohistochemistry, gene overexpression/knockdown | TGF- $\beta$ 1 and HOXA11 were reduced in POP; overexpression/knockdown affected ECM regulation.                       | TGF- $\beta$ 1 and HOXA11 play a key role in ECM remodeling in POP.                  |
| 8  | Ava Leegant et al. (2015)        | Case-control                  | 40 women undergoing vaginal hysterectomy (21 with POP stage $\geq 2$ , 19 controls) | Immunohistochemistry, histological staining         | TGF- $\beta$ 1 and MMP-9 levels were similar in both groups; TGF- $\beta$ 1 increased with age.                        | No direct association between TGF- $\beta$ 1 expression and POP presence.            |
| 9  | Greta Lisa Carlina et al. (2020) | Case-control                  | 100 postmenopausal women (70 with POP stage $\geq 2$ , 30 controls)                 | Immunohistochemistry                                | No significant difference in TGF- $\beta$ 1 expression between groups; higher TGF- $\beta$ 1 in severe prolapse cases. | TGF- $\beta$ 1 expression correlates with POP severity but not with presence of POP. |

## DISCUSSION

Recent investigations into the role of transforming growth factor  $\beta$ 1 (TGF  $\beta$ 1) in pelvic organ prolapse (POP) have produced mixed findings, underscoring the complexity of its involvement in disease pathogenesis. A synthesis of nine studies reveals that TGF  $\beta$ 1's function may vary depending on disease stage, the interplay with other molecular regulators, and methodological differences across studies.

Several studies have reported a significant reduction in TGF  $\beta$ 1 expression in POP patients

compared to controls. For example, research conducted by Ying Zhao et al. (2021), Xiao Ying Qi et al. (2011), Mellie Nur Akin et al. (2021), and Cheng Liu et al. (2017) found that lower levels of TGF  $\beta$ 1 are associated with decreased synthesis of extracellular matrix (ECM) components, such as collagen and elastin, and diminished TIMP2 expression, along with an increase in matrix metalloproteinases (MMP2/9). These findings suggest that insufficient TGF  $\beta$ 1 may impair ECM homeostasis, predisposing pelvic tissues to weakening and eventual prolapse.

Conversely, other studies have not observed significant differences in TGF  $\beta$ 1 levels between POP patients and control groups. Notably, one study found that while overall TGF  $\beta$ 1 levels were similar, patients with severe prolapse exhibited elevated TGF  $\beta$ 1 levels. This observation raises the possibility that TGF  $\beta$ 1 may serve a compensatory function in response to ECM damage in advanced disease stages, highlighting a potential dual role depending on the stage of POP.

Under normal conditions, TGF  $\beta$ 1 facilitates the synthesis of structural proteins like collagen and elastin and helps maintain ECM integrity by inhibiting MMP activity through the upregulation of tissue inhibitors of metalloproteinases (TIMPs).<sup>23</sup> The observed reduction in TGF  $\beta$ 1 in some studies implies that a deficit in this signaling cascade could lead to insufficient ECM repair, thereby contributing to the onset of POP.

In contrast, the increased TGF  $\beta$ 1 levels noted in severe cases might represent an attempted, yet ultimately inadequate, reparative response to extensive ECM degradation. This paradoxical finding suggests that TGF  $\beta$ 1's role in POP is not static but may evolve from a factor in disease initiation to a marker of disease progression as the tissue environment becomes increasingly compromised.

The variability in study outcomes can, in part, be attributed to methodological differences. Variations in analytical techniques—such as immunohistochemistry, Western blotting, or qPCR—can affect the sensitivity and specificity of TGF  $\beta$ 1 measurements. Additionally, the source of tissue samples (e.g., uterosacral ligament versus vaginal tissue) may capture distinct aspects of ECM remodelling, making cross-study comparisons challenging.

Patient demographics further contribute to heterogeneity. Differences in POP staging, age, menopausal status, and the presence of comorbidities such as urgency urinary incontinence can all influence TGF  $\beta$ 1 expression. Moreover, the relatively small sample sizes and potential selection bias—often recruiting from surgical populations that represent more severe cases—limit the statistical power and generalizability of many studies.

To clarify the multifaceted role of TGF- $\beta$ 1 in pelvic organ prolapse (POP), future studies should address several key areas. First, standardization of methodologies is essential. Establishing uniform protocols for tissue sampling and TGF- $\beta$ 1 quantification will help minimize technical variability and facilitate direct comparisons between studies. Consistency in these techniques will enhance the reliability of research findings and promote more accurate conclusions regarding TGF- $\beta$ 1's role in POP.

Second, broadening patient cohorts will improve the representativeness of data. Expanding research to include patients across the full spectrum of POP severity, as well as diverse age groups and hormonal statuses, will provide a more comprehensive understanding of how TGF- $\beta$ 1 expression varies in different populations. Such inclusivity can reveal critical insights into disease progression and patient-specific variations in ECM remodelling.

Third, exploring biomarker networks is crucial for mapping the molecular pathways involved in POP development. Future investigations should examine the interactions between TGF- $\beta$ 1 and

other key regulators such as MMPs, TIMPs, CD44, and HOXA11. These factors play significant roles in ECM homeostasis, and understanding their relationships with TGF- $\beta$ 1 will help elucidate the underlying mechanisms driving tissue weakening in POP.<sup>5</sup>

Fourth, utilizing in vitro and in vivo models can provide deeper mechanistic insights. Employing animal models and cell culture systems will help determine whether changes in TGF- $\beta$ 1 levels are causative of ECM alterations or merely compensatory responses to tissue damage. These models can also be instrumental in testing hypotheses regarding TGF- $\beta$ 1's functional role in POP pathophysiology.

Finally, evaluating therapeutic interventions targeting TGF- $\beta$ 1 may open new avenues for treatment. Investigating whether modulation of TGF- $\beta$ 1 activity can restore ECM balance or prevent disease progression is particularly promising, given the dual role of TGF- $\beta$ 1 in both the initiation and progression of POP. Such studies could lead to novel therapeutic strategies aimed at mitigating the effects of ECM dysregulation in affected patients.

## CONCLUSION

In conclusion, while study results vary, most evidence supports the involvement of TGF- $\beta$ 1 in the pathogenesis of POP through its regulation of the ECM. Reduced TGF- $\beta$ 1 levels may indicate compromised tissue integrity, while elevated levels in severe cases might reflect a failed reparative response.

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## REFERENCES

1. Liu Z, Tang Y, Liu J, Shi R, Houston MA, *et al*, 2023. Platelet-rich Plasma Promotes Restoration of the Anterior Vaginal Wall for the Treatment of Pelvic Floor Dysfunction in Rats J minim Invasiv Gynecol. 30, 45–51. DOI: 10.1016/j.jmig.2022.10.004.
2. Haylen B, Maher C, Barber M, Carnargo S, Dandolu V, *et al*, 2016. An International Urogynecological Association (IUGA) / International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Organ Prolapse (POP). Dalam *Neurourology and Urodynamics* vol. 35 137– 168 Preprint at <https://doi.org/10.1002/nau.22922>. DOI: 10.1007/s00192-015-2932-1.
3. Aboseif C, Liu P, 2022. Pelvic Organ Prolapse. Dalam StatPearls National Library of Medicine.
4. Santoso BI, Fauziah NR, 2017. Prevalence and Characteristics of Pelvic Floor Dysfunction in a Tertiary Care Center in Indonesia. In *Indones J Obstet Gynecol*; 5:3:168-172. DOI: <https://doi.org/10.32771/inajog.v5i3.546>
5. Wu X, Liu X, Li T, 2023. Potential molecular targets for intervention in pelvic organ prolapse. In *Frontiers in Medicine* vol. 10 Preprint at <https://doi.org/10.3389/fmed.2023.1158907>.
6. ZHANG L, DAI F, CHEN G, WANG Y, LIU S, ZHANG L, *et al*. Molecular mechanism of extracellular matrix disorder in pelvic organ prolapses. *Mol Med Rep*. 2020 Dec 1;22(6):4611–8. DOI: <https://doi.org/10.3892/mmr.2020.11564>
7. Peter, P. 2010. Diagnosis of Connective Tissue Damage. in *The Female Pelvic Floor. Function, Dysfunction and Management According to the Integral Theory* 76–117 (Springer, Perth).
8. Lancey D, Jhon OL, 2016. What's new in the functional anatomy of pelvic organ prolapse? Dalam *Current Opinion in Obstetrics and Gynecology* vol. 28 420–429. DOI: <https://doi.org/10.1097/gco.0000000000000312>
9. ZhangT, Li Q, Wang X, Sun Z, 2024. The difference in extracellular matrix metabolism in women with and without pelvic organ prolapse :A systematic review and metaanalysis. Dalam *BJOG; An International Journal of Obstetrics & Gynaecology* 131, 1029–1041. DOI: <https://doi.org/10.1111/1471-0528.17768>
10. Gorlero F, Glorio M, Lorenzi P, Bruno-Franco M, Mazzei C, 2012. New approach in vaginal prolapse repair: Mini-invasive surgery associated with application of platelet-rich fibrin. Dalam *Int Urogynecol J* 23, 715– 722. DOI:10.1007/s00192-012-1667-5
11. Deng ZM, Dai FF, Yuan MQ, Yang DY, Zheng YJ, Cheng YX. Advances in molecular mechanisms of pelvic organ prolapse (Review). *Exp Ther Med*. 2021 Jul 15;22(3). DOI: 0.3892/etm.2021.10442.
12. Carlin GL, Bodner K, Kimberger O, Haslinger P, Schneeberger C, Horvat R, *et al*. The role of transforming growth factor- $\beta$  (TGF- $\beta$ 1) in postmenopausal women with pelvic organ prolapse: An immunohistochemical study. *Eur J Obstet Gynecol Reprod Biol X*. 2020 Jul 1;7.DOI: 10.1016/j.eurox.2020.100111
13. Sugaya K, Kadakewa K, Ashitomi K, Nishijima S, Seiji M, 2023. Plasma Levels of Transforming Growth Factor-Beta 1 in Women with Pelvic Organ Prolapse. In *Scientific Research. Open Journal of Urology*, 13: 133-142. <https://doi.org/10.4236/oju.2023.135017>

14. Kong M, Wang Z, Hao Y, Shi Y, Yang X, *et al*, 2025. Role of the integrin  $\alpha 1$ / TGF- $\beta 1$  signaling pathway in the pathogenesis of pelvic organ prolapse; A study on vaginal wall tissue alterations and molecular dysfunction. In *Molecular Medicine Reports*, 31: 104. <https://doi.org/10.3892/mmr.2025.13469>
15. Zhao Y, Xia Z, Lin T, Qin M. Transforming growth factor beta 1 and p44/42 expression in cardinal ligament tissues of patients with pelvic organ prolapse. *Medical Science Monitor*. 2021;27. DOI: 10.12659/MSM.930433
16. Qi XY, Hong L, Guo FQ, Fu Q, Chen L, Li BS. Expression of transforming growth factor-beta 1 and connective tissue growth factor in women with pelvic organ prolapse [Internet]. Vol. 32, *Saudi Med J*. 2011. DOI: 10.12659/MSM.930433
17. Akin MN, Sivaslioglu AA, Edgunlu T, Kasap B, Celik SK. SMAD2, SMAD3 and TGF- $\beta$  GENE expressions in women suffering from urge urinary incontinence and pelvic organ prolapse. *Mol Biol Rep*. 2021 Feb 1;48(2):1401–7. <https://doi.org/10.62347/LXZT1726%0D>
18. Liu C, Wang Y, Li BS, Yang Q, Tang JM, Min J, *et al*. Role of transforming growth factor  $\beta$ -1 in the pathogenesis of pelvic organ prolapse: A potential therapeutic target. *Int J Mol Med*. 2017 Aug 1;40(2):347–56. <https://doi.org/10.3892/ijmm.2017.3042>
19. Vetuschi A, Pompili S, Gallone A, D'Alfonso A, Carbone MG, Carta G, *et al*. Immunolocalization of advanced glycation end products, mitogen activated protein kinases, and transforming growth factor- $\beta$ /Smads in pelvic organ prolapse. *Journal of Histochemistry & Cytochemistry*. 2018 Sep;66(9):673–86. <https://doi.org/10.1369/0022155418772798>
20. Ying W, Hu Y, Zhu H. Expression of CD44, Transforming Growth Factor- $\beta$ , and Matrix Metalloproteinases in Women With Pelvic Organ Prolapse. *Front Surg*. 2022 Jul 15;9. <https://doi.org/10.3389/fsurg.2022.902871>
21. Leegant A, Zuckerwise LC, Downing K, Brouwer-Visser J, Zhu C, Cossio MJ, *et al*. Transforming growth factor  $\alpha 1$  and extracellular matrix protease expression in the uterosacral ligaments of patients with and without pelvic organ prolapse. *Female Pelvic Med Reconstr Surg*. 2015;21(1):53–8. DOI: 10.1097/SPV.0000000000000130
22. Carlin GL, Bodner K, Kimberger O, Haslinger P, Schneeberger C, Horvat R, *et al*. The role of transforming growth factor- $\beta$  (TGF- $\beta 1$ ) in postmenopausal women with pelvic organ prolapse: An immunohistochemical study. *Eur J Obstet Gynecol Reprod Biol X*. 2020 Jul 1;7. DOI ; 10.1016/j.eurox.2020.100111
23. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, *et al*. The Roles of Matrix Metalloproteinases and Their Inhibitors in Human Diseases. *Int J Mol Sci*. 2020 Dec 20;21(24):9739. <https://doi.org/10.3390/ijms21249739>