Impact of prolapse meshes on the metabolism of vaginal extracellular matrix in rhesus macaque

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OBJECTIVE: The impact of polypropylene mesh implantation on vaginal collagen and elastin metabolism was analyzed using a nonhuman primate model to further delineate the mechanism of mesh induced complications.

STUDY DESIGN: Forty-nine middle-aged parous rhesus macaques underwent surgical implantation of 3 synthetic meshes via sacrocolpopexy. Gynemesh PS (n = 12) (Ethicon, Somerville, NJ) and 2 lower-weight, higher-porosity, lower-stiffness meshes (UltraPro [n = 19] [Ethicon] and Restorelle [n = 8] [Coloplast, Minneapolis, MN]) were implanted, in which UltraPro was implanted with its blue orientation lines perpendicular (low stiffness direction, n = 11) and parallel (high stiffness direction, n = 8) to the longitudinal axis of the vagina. Sham-operated animals were used as controls (n = 10). Twelve weeks after surgery, the mesh-tissue complex was excised and analyzed.

RESULTS: Relative to sham, Gynemesh PS had a negative impact on the metabolism of both collagen and elastin—favoring catabolic reactions, whereas UltraPro induced an increase only in elastin degradation. Restorelle had the least impact. As compared with sham, the degradation of collagen and elastin in the vagina implanted with Gynemesh PS was increased with a simultaneous increase in active matrix metalloproteinase (MMP)-1, -8, -13, and total MMP-2 and -9 (all $P < .05$). The degradation of elastin (tropoelastin and mature elastin) was increased in the UltraPro-implanted vagina with a concomitant increase of MMP-2, and -9 (all $P < .05$). Collagen subtype ratio III/I was increased in Gynemesh PS and UltraPro perpendicular groups ($P < .05$).

CONCLUSION: Following implantation with the heavier, less porous, and stiffer mesh, Gynemesh PS, the degradation of vaginal collagen and elastin exceeded synthesis, most likely as a result of increased activity of MMPs, resulting in a structurally compromised tissue.

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Background and Objective

Mesh-related complications including mesh exposure through the vaginal wall and erosion into adjacent structures, pain, and infection have raised concerns, prompting the Food and Drug Administration to issue 2 public health notifications warning of complications related to prolapse mesh and calling for mechanistic studies.

In a well-controlled nonhuman primate sacrocolpopexy model, heavier-weight, lower-porosity, and higher-stiffness meshes were shown to have a profoundly negative impact on the vagina, including a decrease in the amount of collagen, elastin, and smooth muscle. The resulting thinner and biomechanically inferior vagina seemed a perfect scenario for the development of mesh exposure.

In this study, we aimed to define alterations in collagen and elastin metabolism following the implantation of synthetic meshes varying by weight, porosity, and stiffness. The heavier, less porous, and stiffer prolapse mesh (Gynemesh PS; Ethicon, Somerville, NJ) vs 2 lighter, more porous, and less stiff meshes with (UltraPro; Ethicon) and without (Restorelle; Coloplast, Minneapolis, MN) an absorbable component, poliglecaprone 25, were implanted via sacrocolpopexy in the rhesus macaque. Because UltraPro is highly anisotropic, it was implanted with its blue orientation lines perpendicular (low stiffness direction) and parallel (high stiffness direction) to the longitudinal axis of the vagina.

Materials and Methods

Thirty-nine animals were implanted with mesh via sacrocolpopexy after hysterectomy: Gynemesh PS (n = 12), UltraPro Perpendicular (n = 11), UltraPro Parallel (n = 8), and Restorelle (n = 8). Ten animals underwent the identical surgery (sham) without insertion of mesh (n = 10). Twelve weeks later, the mesh-tissue complex was harvested and the epithelium carefully removed prior to biochemical analyses.

Following extraction using a high salt buffer (pH 7.5), proteins at 10 μg/well were separated on 8% polyacrylamide gels and examined with Western blot, including COL1A1, COL3A1,

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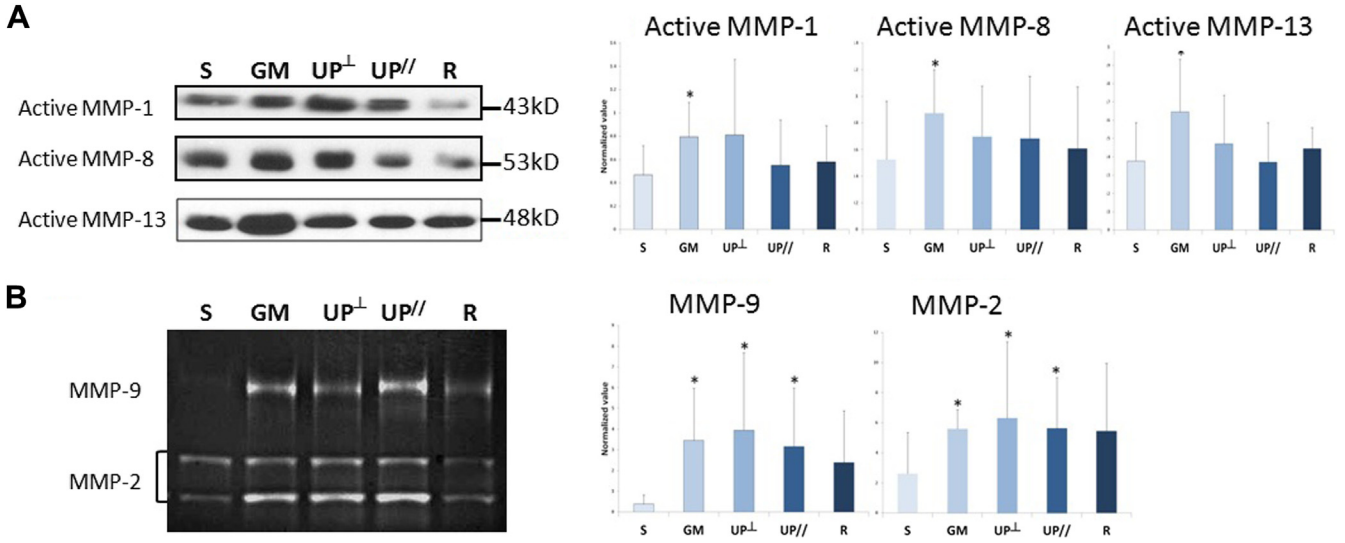
FIGURE
Levels of MMPs after mesh implantation



A, Interstitial collagenase MMP-1, -8, and -13. **B,** Elastase MMP-2 and -9 in the vagina after mesh implantation demonstrated by representative images from Western blots and zymography and bar graphs showing compiled mean (normalized to the values of internal control and loading control) and SD. *Asterisk* indicates a significant difference from sham ($P < .05$).

Gynemesh PS; Ethicon, Somerville, NJ. UltraPro; Ethicon. Restorelle; Coloplast, Minneapolis, MN.

GM, Gynemesh PS; *MMP*, matrix metalloproteinase; *R*, Restorelle; *S*, sham; *UP⊥*, UltraPro Perpendicular; *UP//*, UltraPro Parallel.

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tropoelastin, tropoelastin degradation products, and matrix metalloproteinases (MMPs)-1, -8, and -13. The level of elastin-degrading enzymes MMP-2 and -9 was evaluated via substrate zymography. In the less than 30 kDa peptide solution, the amount of cross-linked N-telopeptides was measured to represent degradation of mature collagen. The amount of desmosine was measured via desmosine cross-link radioimmunoassay to represent degradation of mature elastin. After protein extraction, salt-insoluble tissue pellets were used to determine the ratio of collagen subtypes III/I.

RESULTS

Collagen I precursors were significantly increased in all mesh groups relative to sham, with an increase of 66%, 63%, 46%, and 43% in Gynemesh PS ($P = .014$), UltraPro Perpendicular ($P = .023$), UltraPro Parallel ($P = .026$), and Restorelle ($P = .018$), respectively. Collagen III precursors increased 26% with Gynemesh PS ($P = .03$) and 29% with UltraPro Perpendicular ($P = .005$); no differences were found in the other mesh groups relative to sham (all $P > .05$). Collagen III precursors were 45% higher in the UltraPro Perpendicular than the UltraPro Parallel group ($P = .004$).

Relative to sham (0.20 ± 0.05), the ratio of collagen subtype III/I was 66% higher in Gynemesh PS (0.33 ± 0.04, $P < .001$) and 55% higher in UltraPro Perpendicular (0.31 ± 0.06, $P < .001$). A comparison between the 2 UltraPro groups showed that the ratio was 26% higher in the perpendicular orientation than that in the parallel orientation ($P = .03$).

Collagen degradation was increased by 62% in the Gynemesh PS group relative to sham ($P = .007$), whereas the other mesh groups were not statistically different from sham (all $P > .05$). Tropoelastin degradation was increased in all mesh groups relative to sham, with the highest degradation in the Gynemesh PS group (119%, $P = .007$), followed by UltraPro Parallel (93%, $P = .015$), Restorelle (77%, $P = .042$), and UltraPro Perpendicular (71%, $P = .009$). Mature elastin degradation was increased in Gynemesh PS, UltraPro Perpendicular, and UltraPro Parallel relative to sham by an average increase of 76% ($P = .049$), 136% ($P = .006$), and 98% ($P = .025$), respectively, but not in the Restorelle group ($P = .589$).

Active MMP-1, -8, and -13 were significantly increased in the Gynemesh PS group compared with sham, with MMP-1 increased by 70% ($P = .014$), MMP-8 by 66% ($P = .048$), and MMP-13 by 71% ($P = .011$). In contrast, the amount of these MMPs was not different from sham in the lighter, more porous UltraPro and Restorelle (all $P > .05$) (Figure, A). No difference was found between the UltraPro groups (all $P > .05$).

When compared with sham, total MMP-2 increased considerably following the implantation of Gynemesh PS, UltraPro Perpendicular, and UltraPro Parallel by 114% ($P = .003$), 141% ($P = .046$), and 116% ($P = .045$), respectively, but not with Restorelle ($P = .11$) (Figure,

B). Total MMP-9 increased in Gynemesh PS, UltraPro Perpendicular, and UltraPro Parallel by 796% ($P = .007$), 925% ($P = .003$), and 719% ($P = .028$), respectively, but not in Restorelle ($P = .109$). No difference was found between the UltraPro groups (all $P > .05$).

Comment

Heavier, less porous, stiffer mesh was associated with increased matrix degradation. Meshes of lower weight, higher porosity, and lower stiffness had a less negative impact.

Polypropylene implanted in humans incites a classic foreign body response. Levels of activated MMP-1, -2, -8, -9, and -13 increased after the implantation of Gynemesh PS, correlating well with our previous observation that Gynemesh PS induced stronger foreign body inflammatory responses than meshes of lower weight, higher porosity, and lower stiffness. Because the inflammatory reaction becomes stronger in proportion to the amount of material implanted, an increased mesh burden seems more likely to induce prolonged activation of MMPs and excessive matrix destruction.

Mesh stiffness is a second critical parameter that affects tissue response by conferring inappropriate mechanical loading to the vagina. Our finding that higher stiffness Gynemesh PS induced the highest levels of MMPs is also in line with this phenomenon.

The persistent elevated ratio of collagen type III to I in the vagina 3 months after the implantation of Gynemesh PS and UltraPro Perpendicular indicates the presence of prolonged stimuli, possibly from chronic tissue injury caused by a gradual deformation/micromotion of mesh fibers under the loading conditions. Thus, the less negative impact of UltraPro Parallel and Restorelle on the vagina highly suggests that the stability of pore geometry with loading is also an important factor for mesh-tissue responses.

CLINICAL IMPLICATIONS

- Relative to lighter, more porous, less stiff meshes, implantation with heavier, less porous, stiffer mesh such as Gynemesh PS may weaken the vaginal wall by inducing catabolic responses of matrix protein, predisposing to mesh exposure development.
- The stability of mesh pore geometry with loading, in addition to weight, porosity, and stiffness, should be considered in the selection of prolapse mesh. ■