**Charles University in Prague, Third Faculty of Medicine, Institute for the Care of Mother and Child**

**&**

**University of Leuven, Doctoral school of Medical Sciences**

Thesis autoreferate

# MODERN TECHNLOGIES IN THE ASSESMENT AND TREATMENT OF PELVIC ORGAN PROLAPSE
# –
# CLINCIAL AND EXPERIMENTAL STUDY AIMS

**MUDr. Urbankova Iva**

Prague 2017

**Doctoral programs in Biomedicine**

*Charles University in Prague*
*and Academy of Sciences of Czech Republic*

**Specialization**: Experimental surgery
**Chair:** Prof. MUDr. Jaroslav Živný, DrSc.

**Research center:**
Institute for the Care of Mother and Child
Department of Development and Regeneration, KU Leuven

Jury:
Promoters: Prof. Dr. Jan Deprest
Doc. MUDr. Ladislav Krofta, CSc.
Chair: Prof. Dr. Dirk Timmerman
Prof. Dr. Tania Roskams
Secretary: Prof. Dr. Frank Van der Aa
Jury members: Prof. Dr. André D´Hoore
Prof. Dr. Laurent de Landsheere
Prof. Dr. Stefano Salvatore
Prof. MUDr. Jaromír Mašata CSc.
Prof. BSc. Sheila MacNeil
Prof. MUDr. David Kachlík, PhD
Thesis autoreferate was delivered on:

**TABLE OF CONTENT:**

## SUMMARY IN CZECH

Tento projekt ukázal, že sestup pánevních orgánů spojen jednak s poraněními pánevního dna vzniklými v průběhu vaginálního porodu a jednak s věkem rodičky. Již jeden rok po porodu lze až u každá osmá žena identifikovat významný sestup. Ženy, které utrpěly poranění svalů pánevního dna, jsou vystaveny riziku časnějšího vzniku sestupu. Proto, abychom zlepšili naše znalosti o vývoji a chirurgické léčbě sestupu pánevních orgánů, jsme podrobněji studovali ovčí model. Identifikovali jsme anatomické a morfologické podobnosti a také popsali změny poševní stěny vyvolané specifickými životními událostmi (první porodu, uměle vytvořená menopauza či hormonální substituční terapie), které jsou podobné změnám popisovaným u žen. Ovčí model jsme dále použili pro testování nových implantátů a zobrazovacích technik. Věříme, že ovčí model je možné v budoucnosti použít pro studium patofyziologie sestupu pánevních orgánů a pro testování nových léčebných metod a postupů.

## SUMMARY IN ENGLISH

This project has shown that pelvic organ prolapse is linked with maternal age and delivery-related injuries. Up to every eight women may have a symptomatic prolapse already one year after their first delivery. Moreover, those with muscle injury have a higher short-term risk of pelvic organ prolapse development. To improve our knowledge

we further explored the potential of an ovine model for prolapse and vaginal surgery. We showed that many anatomical and morphological features and vaginal wall changes induced by specific lifespan factors (first delivery, artificial menopause, and hormonal replacement) are similar to what is observed in women. We further used this model for testing novel implants and mesh visualization techniques. We believe that the ovine model can be used in future research on pelvic organ prolapse pathophysiology and novel treatment modalities.

## SAMENVANTTING

Samengevat heeft ons studiewerk aangetoond dat vaginale verzakking klinisch gelinkt is aan een hogere leeftijd bij eerste bevalling en aan geboorte-trauma. Een op acht vrouwen had een symptomatische prolaps binnen het eerste jaar na de bevalling. Wanneer er levator avulsie was, waren de gevolgen meer uitgesproken. In het translationeel onderzoeksgedeelte onderzochten we de bruikbaarheid van het schapenmodel voor fysiologisch onderzoek evenals voor experimenteel chirurgische studies. We toonden aan dat er veel anatomische en morfologische gelijkenissen zijn. Bepaalde gebeurtenissen, zoals eerste vaginale bevalling, artificiële menopause en hormoon vervangingstherapie, hebben gelijkaardige effecten op de vagina van de ooi, als wat wordt vastgesteld bij de mens. We hebben dit diermodel gebruikt voor het testen van specifieke vaginale implantaten, zoals PVDF-implanten die op MR zichtbaar zijn. Samengevat denken we dat dit schapenmodel verder gebruikt kan worden in het onderzoek naar oorzaken en oplossingen van bekkenbodemproblemen

## INTRODUCTION

Pelvic floor dysfunctions (PFD) encompass pelvic organ prolapse (POP), urinary and faecal incontinence, as well as sexual dysfunction. PFD reduces quality of life and its impact is as severe as Parkinson’s disease or tension headache [1]. POP is characterized by protrusion of the vaginal wall and descent of organs from their original location. Prolapse affects one in two women who delivered vaginally, half of them being symptomatic [2]. The pathogenesis of PFD is multifactorial, which has been depicted by DeLancey et al in an integrated life span model [3] (Fig 1). It describes the complex interplay between genetic factors, vaginal birth-induced trauma, aging, lifestyle and other factors [3]. This model is supported with observational studies which also introduced further risk factors such as maternal age at first delivery, infant weight, degree of perineal injury or current BMI [2,4]. Additional risk factors for PFD are avulsion of the levator ani or endopelvic fascia [5,6]. Further deterioration of pelvic floor is related to aging accelerated by estrogen deficiency after menopause [7].

Surgery is the mainstay of therapy with 19% of women undergoing surgery by the age of 80 years [8]. It aims to restore anatomical support while preserving the vaginal function. Originally, these surgeries repair site specific anatomical defects in the anterior and posterior repairs using the surrounding “native” tissue. However, these repairs have an up to 29% recurrence rate mainly because of the insufficient tissue quality used for the repair [9] . This has led to the use of permanent synthetic materials, either used as flat sheets or secured and anchored by using prosthetic arms or anchors. In the anterior compartment these repairs decrease the anatomical failure rate [10] , however data on posterior prolapse is limited and inconsistent [10]. While these meshes perform the intended goal of restoring anatomical support, their use is associated with a number of graft- related complications (GRCs) which may be as frequent as 10% [11]. Following vaginal insertion these meshes are more likely to lead to mesh exposure, contraction, pain or infection. Additional GRCs may be induced by the mesh fixation method, such as introducing the anchors or long prosthetic arms. These fixations passage of arms, are often through dense structures to help maintain support of the mesh but can also cause direct injury or secondary pain [12]. Control data on local complications following native tissue repairs are nearly lacking, in essence because the problem received initially not much attention, and standardization of terminology was only introduced in 2012 [13]. The US Food and Drug Administration issued a health notification in 2011 on the importance of researching the development, incidence, prevention and management of GRCs. Additionally the International UroGynaecologic Association (IUGA) suggested that appropriate animal experimentation should be part of the production cycle of novel meshes [14].

Typically, animal studies are dedicated to characterizing the host response to implants yet should be done in relevant models for vaginal surgery. The rabbit model, which we as well as others often used because it is considered as a large animal, obviously does not mimic all conditions present during vaginal surgery. Even in ideal circumstances, rabbit vaginal explants are relatively small, which makes appropriate uniaxial and, certainly, biaxial testing of the implants difficult to perform [15]. So there was still a need for appropriate “vaginal” models. Non-human primates can be used to mimic prolapse and pelvic floor surgery but ethical concerns represent obvious obstacles, certainly in Europe [16]. De Tayrac et al. proposed the ewe as large animal model for experimental vaginal surgery [17]. We then used it to describe contraction and exposure rates as well as biomechanical properties of different natures and sizes of implants. Since ewes may suffer of spontaneous pelvic organ prolapse [18], we hypothesized that sheep may serve as a good large animal model.

## SPECIFIC STUDY AIMS:

The **clinical study** was completed in the Institute for the Care of Mother and Child, Third Faculty of Medicine of the Charles University in Prague, Czech Republic. This prospective cohort study aims andy hypothesis:

- Aim: To determine the occurrence of, and major risk factors for pelvic floor dysfunction among primiparous women one year after delivery.
- Hypothesis: Pregnancy and vaginal delivery have adverse effect on the pelvic floor function one year postpartum. Women in higher risk of pelvic floor dysfunction could be identified before and shortly after the first delivery.

**Experimental work** was done at the Centre for Surgical Technologies of the Group Biomedical Sciences, KU Leuven, Belgium and was dedicated to the description of, and experiments in a large animal model for vaginal surgery. These studies more specifically aimed to:

- Aim: To characterize the pelvic floor anatomy of the virgin ewe and compared it to that of women.
- Hypothesis: Sheep pelvic have to certain extent similar to the female pelvis and

therefore could be used as a model for prolapse and vaginal surgery.

- Aim: To document the effects of certain key events in the lifespan of women, such as their first delivery and menopause or while under its replacement therapy.
- Hypothesis: Lifespan events such as first delivery, ovariectomy and hormonal replacement therapy changes morphology and biomechanical properties of the ovine vaginal wall.

- Aim: To compare biocompatibility of an acellular collagen matrix as an alternative to a polypropylene *flat* mesh augmented transvaginal repair.
- Hypothesis: Biocompatibility of an acellular collagen matrix derived from the bovine pericardium is comparable to polypropylene implant.

- Aim: To establish an ovine model for trocar guided transvaginal insertion of mesh with anchors, representative of the procedures clinically used.
- Hypothesis: Trocar guided insertion of mesh anchored with arms in the ovine rectovaginal septum is possible.

- Aim: To document the in vivo deformation of anchored implants as compared to flat meshes using a magnetic resonance imaging and computerized image analysis.

- Hypothesis: In vivo behaviour, deformation and position of arm anchored implant inserted in the ovine rectovaginal septum is similar to a rectangular mesh secured with interrupted sutures to the underlying tissue.

## MATERIAL AND METHODS

In the clinical part (Chapter 2), we prospectively followed a cohort of nulliparous women with uncomplicated singleton pregnancy, who delivered vaginally. Urogynecological assessment at six weeks and twelve months included objective and subjective evaluation of the pelvic floor anatomy and function, and two validated questioners. Collected demographic and obstetrical data were used in an uni- and multivariate regression analysis to determine the risk factors for urinary incontinence, POP and the levator ani injury.

In the experimental part we used Swifter ewes provided by the Zoötechnical Institute of the KU Leuven (Lovenjoel, Belgium) (Chapters 3-7). Their age and parity depended on each specific study. All experiments were approved by the Ethics Committee for Animal Experimentation of the Faculty of Medicine of the K.U. Leuven. All applicable international, national and institutional guidelines for the housing, care and use of animals were followed.

Comparative anatomical study aimed to describe the nulliparous ovine pelvic floor anatomy and compare it to that in women (Chapter 3). Anatomical dissections were carried on fresh and fixed specimens, and a plastinated and 3D magnetic-resonance-based model were obtained.

Other experimental studies were carried on groups of animals (6-10 ewes). In Chapter 4 we used a group of nulliparous, primiparous and multiparous ewe. The latter were ovariectomized and half of them received an estradiol hormonal replacement therapy [13] .

Two other experimental studies evaluated a biocompatibility and biomechanical behaviour of two novel implants. In Chapter 5 we used a cross-linked acellular collagen matrix (ACM) as an alternative to a polypropylene implant. In Chapters 7, implants were fabricated from polyvinidylne flouride loaded with the iron particles. One implant was rectangular (so called “flat”) mesh and the other had its central rectangular part extended with two pairs of anchoring arms (H-shaped). In these studies implants were inserted in the in the ovine rectovaginal septum under sterile conditions and animals were followed for 180 and 60 das, respectively. Surgical procedure in Chapter 7 was tested in a small feasibility study and also recorded for educational purposes (Chapter 6).

The outcome in Chapter 4, 5 and 7 included the macro- and microscopical evaluation of tissues and implants, and active and passive biomechanics. Histological evaluation aimed to detect changes in the tissue composition (collagen content, organization etc.) or the immune response to implants (polymorphonuclears, foreign body giant cells etc.) The active biomechanics represent the in vivo tissue properties of the vaginal wall, specifically the contractility of smooth muscle cells. This is done in the contractility assay, in which the tissue specimens placed in oxygenated Krebs solution are exposed to KCl and generated contractile forces are measured [14]. The passive biomechanics describe the ex vivo properties when exposed to the load. We used either the ball burst test or the uniaxial tensiometry [15].

In Chapter 7 we used implants loaded with the iron particles that allowed their visualization on the magnetic resonance (MR). During the follow up period animals underwent three consecutive MR scans. data were used to reconstruct the in vivo shape of the implant to compare longitudinally their shape, position and thickness [16].

## RESULTS

The clinical study was conducted in Prague, Czech Republic, and included a cohort of 987 nulliparous women who delivered vaginally. One year after delivery one-third of women reported urinary incontinence, 13% had pelvic organ prolapse reaching down to the level of hymen or beyond and 3.3% reported anorectal dysfunction mainly painful defecation. Following their first delivery, 18% of women sustained levator ani avulsion and 17% had levator hiatus ballooning. Both have been named to be closely related to the further development of symptomatic pelvic organ prolapse and its recurrence after surgical correction. In our study, also age and body mass index increased the likelihood of urinary incontinence, whereas age also increased the risk for pelvic organ prolapse. Risk factors for levator ani avulsion included forceps delivery, whereas epidural analgesia and perineal rupture grade I were ‘protective’.

In the sheep model, we first characterized the pelvic floor anatomy of the virgin ewe and compared it to that of women. Second, we documented the effects of certain key lifespan events such as the first delivery, menopause and the changes after hormone replacement therapy. We identified many anatomical and structural similarities such as vaginal dimensions, the composition of the vaginal wall, and the attachments of levator ani muscle.

Some anatomical structures present in women are not developed in sheep (i.e. the sacrospinous ligament, internal obturator muscle and obturator membrane) and their pelvic floor anatomy seems to be adapted to their quadruped position and presence of a tail. We demonstrated the effects of specific lifespan events (first vaginal delivery, ovariectomy, hormonal replacement therapy) on active and passive biomechanical properties of the ovine vagina. Following first vaginal delivery, the ovine vagina became more spacious, its distal part becomes less stiff and smooth muscles generate lower contractile forces. Following artificially induced menopause the ovine vagina was narrower and its middle part becomes stiffer. Estradiol hormonal replacement returned the stiffness within the range of the premenopausal animal. Histology showed only a limited amount of changes, comparable to those seen in women, yet to us, these do not sufficiently explain the biomechanical changes.

The experimental work was also dedicated to the study of the effect of novel implants in the treatment of pelvic organ prolapse. In a comparative study, we used a bovine-derived acellular cross-linked collagen matrix (ACM) suggested as an alternative to polypropylene "flat" meshes. Both types of implants were inserted in the ovine rectovaginal septum. After 6 months, ACMs showed more local graft-related complications and biomechanical properties comparable to polypropylene. Moreover, partial degradation of ACM had a negative impact on smooth muscle contractility. We concluded that ACM does not seem to have a better biosafety profile than polypropylene.

To proceed with the experimental study of certain vaginal repairs in sheep, we first needed to further explore the potential and feasibility of an implant that can be anchored via additional arms within the pelvis. In a small study, we performed a trocar guided transvaginal insertion of a purpose made H-shaped implant to fit ovine anatomy and dimensions. No serious complications were identified. We also made the surgical procedure as a video document for educational purposes.

In a subsequent study, the previously described H-shaped mesh and flat mesh were implanted. Both meshes are made from polymeric polyvinidylene fluoride loaded with iron particles which allow its visualization with magnetic resonance (MR). In a longitudinal study, we collected data documenting the stability of the shape and position of the implants. Initially, there was a drop in the effective surface area in both types of implants, where after the area remained stable until the end of the observational period. More detailed analysis of thickness maps obtained from MRI data revealed two deformations patterns, different for the H-shape and flat mesh. Deformation of H-shaped implants was most probably due to distinct biomechanical properties of its central part and arms, whereas flat implants displayed a heterogenic pattern most probably linked with pore aggregation caused by suturing. The implants were well tolerated with a low rate of graft-related complications, the absence of an effect on smooth muscle contractility yet there was an increase in stiffness of the augmented tissue.

## DISCUSSION AND CONCLUSIONS

In general, this project has shown that pelvic organ prolapse is linked with maternal age and delivery-related injuries. Up to every eight women may have a symptomatic prolapse already one year after their first delivery. Moreover, those with muscle injury have a higher short-term risk of pelvic organ prolapse development. To improve our knowledge we further explored the potential of a large ovine model for prolapse and vaginal surgery. We showed that many anatomical and morphological features and vaginal wall changes induced by specific lifespan factors (first delivery, artificial menopause, and hormonal replacement) are similar to what is observed in women. We further used this model for testing novel implants and mesh visualization techniques. We believe that the ovine model can be used in future research on pelvic organ prolapse pathophysiology and novel treatment modalities.

.

**REFFERENCES:**


1. Hunskaar S, Vinsnes A (1991) The quality of life in women with urinary incontinence as measured by the sickness impact profile. J Am Geriatr Soc 40:976–7.
2. Glazener C, Elders A, MacArthur C, et al. (2013) Childbirth and prolapse: Long-term associations with the symptoms and objective measurement of pelvic organ prolapse. BJOG An Int J Obstet Gynaecol 120:161–168. doi: 10.1111/1471-0528.12075
3. DeLancey JOL, Kane Low L, Miller JM, et al. (2008) Graphic integration of causal factors of pelvic floor disorders: an integrated life span model. Am J Obstet Gynecol 199:610.e1-5. doi: 10.1016/j.ajog.2008.04.001
4. Gyhagen M, Bullarbo M, Nielsen TF, Milsom I (2013) Prevalence and risk factors for pelvic organ prolapse 20 years after childbirth: A national cohort study in singleton primiparae after vaginal or caesarean delivery. BJOG An Int J Obstet Gynaecol 120:152–160. doi: 10.1111/1471-0528.12020
5. Rizk DEE, Fahim M a. (2008) Ageing of the female pelvic floor: Towards treatment a la carte of the "geripause." Int Urogynecol J Pelvic Floor Dysfunct 19:455–458. doi: 10.1007/s00192-008-0576-0
6. Maher C, Feiner B, Baessler K, Schmid C (2013) Surgical management of pelvic organ prolapse in women ( Review ) Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. doi: 10.1002/14651858.CD004014.pub5.Copyright
7. Jia X, Glazener C, Mowatt G, et al. (2010) Systematic review of the efficacy and safety of using mesh in surgery for uterine or vaginal vault prolapse. Int Urogynecol J 21:1413–31. doi: 10.1007/s00192-010-1156-7
8. Haylen BT, Freeman RM, Swift SE, et al. (2011) An International Urogynecological Association ( IUGA ) / International Continence Society ( ICS ) joint terminology and classification of the complications related directly to the insertion of prostheses ( meshes , implants , tapes ) & grafts in female pe. Int Urogynecol J 22:3–15. doi:

10.1007/s00192-010-1324-9
9. Slack M, Ostergard D, Cervigni M, Deprest J (2012) A standardized description of graft-containing meshes and recommended steps before the introduction of medical devices for prolapse surgery. Consensus of the 2nd IUGA Grafts Roundtable: optimizing safety and appropriateness of graft use in transvaginal pe. Int Urogynecol J 23 Suppl 1:S15-26. doi: 10.1007/s00192-012-1678-2
10. Ozog Y, Mazza E, De Ridder D, Deprest J (2012) Biomechanical effects of polyglecaprone fibers in a polypropylene mesh after abdominal and rectovaginal implantation in a rabbit. Int Urogynecol J 23:1397–402. doi: 10.1007/s00192-012-1739-6
11. Otto L, Slayden DO, Clark A (2002) The rhesus macaque as an animal model for pelvic organ prolapse. Am J Obstet Gynecol 186:416–421. doi: 10.1067/mob.2002.121723
12. de Tayrac R, Alves A, Thérin M (2007) Collagen-coated vs noncoated low-weight polypropylene meshes in a sheep model for vaginal surgery. A pilot study. Int Urogynecol J Pelvic Floor Dysfunct 18:513–20. doi: 10.1007/s00192-006-0176-9
13. Brasted M, White C, Kennedy T, Salamonsen L (2003) Mimicking the events of menstruation in the murine uterus. Biol Reprod 69:1273–80. doi: 10.1095/biolreprod.103.016550
14. Feola A, Endo M, Urbankova I, et al. (2015) Host reaction to vaginally inserted collagen containing polypropylene implants in sheep. Am J Obstet Gynecol 212:474.e1-474.e8. doi: 10.1016/j.ajog.2014.11.008
15. Feola A, Barone W, Moalli P, Abramowitch S (2012) Characterizing the ex vivo textile and structural properties of synthetic prolapse mesh products. Int Urogynecol J 1–6. doi: 10.1007/s00192-012-1901-1
16. Sindhwani N, Feola A, De Keyzer F, et al. (2015) Three-dimensional analysis of implanted magnetic-resonance-visible meshes. Int Urogynecol J 26:1459–1465. doi: 10.1007/s00192-015-2681-1

## PUBLICATION ACTIVITY RELATED TO DISSERTATION WITH THE IMPACT FACTOR:

- Endo M, Urbankova I, Vlacil J, Sengupta S, Deprest T, Klosterhalfen B, Feola A, Deprest J. Cross-linked xenogenic collagen implantation in the sheep model for vaginal surgery. Gynecol Surg [Internet]. 2015; 113–22; doi: 10.1007/s10397-015-0883-7, **IF 0.38**
- Urbankova I, Vdoviakova K, Rynkevic, R, Sindhwani N, Deprest D, Feola A, Herijgers P, Krofta L, Deprest J, Comparative anatomy of the ovine and female pelvis; Gynecol Obstet Invest. 2017; Jan 27; doi: 10.1159/000454771**, IF 1.67**
- Urbankova I, Callewaert G, Sindhwani N, Turri A, Hympanova L, Feola A, Deprest J, Transvaginal Mesh Insertion in the Ovine Model. J Vis Exp. 2017; Jul (27);(125); doi: 10.3791/55706, **IF 1.2**
- Urbankova I, Sindhwani N, Callewaert G, Turri A, Rinkijevic R, Hympanova L, Feola A, Deprest J, In vivo documentation of shape and position changes of MRI-visible mesh placed in t rectovaginal septum. J Mech Behav Biomed Mater. 2017 Nov (75), 379 – 89, doi: 10.1016/j.jmbbm.2017.08.005, **IF 1.96**

## OTHER PUBLICATIONS WITH THE IMPACT FACTOR:

- Sindhwani N, Feola A, De Keyzer F, Claus F, Callewaert G, Urbankova I, Ourselin S, D´hooge J, Deprest J. Three-dimensional analysis of implanted magnetic-resonance-visible meshes. Int Urogynecol J [Internet]. 2015;26(10):1459–65. Doi: 10.1007/s00192-015-2681, **IF 1.96**
- Feola A, Endo M, Urbankova I, Vlacil J, Deprest T, Bettin S, Klosterhalfen B, Deprest J. Host reaction to vaginally inserted collagen containing polypropylene implants in sheep. Am J Obstet Gynecol [Internet]. Elsevier; 2015 Dec 11;212(4): 474.e1–474.e8. doi: 10.1016/j.ajog.2014.11.008, **IF 4.7**
- Sindhwani N, Liaquat Z, Urbankova I, Vande Velde G,

Feola A, Deprest J. Immediate postoperative changes in synthetic meshes – In vivo measurements. J Mech Behav Biomed Mater [Internet]. Elsevier; 2015; 55: 228–3; doi: 10.1016/j.jmbbm.2015.10.015, **IF 2.87**

- Sabiniano R, Urbankova I, Callewaert G, Lesage F, Hillary C, Osman NI, Cappele R, Deprest J, MacNeil S. Evaluating Alternative Materials for the Treatment of Stress Urinary Incontinence and Pelvic Organ Prolapse: A Comparison of the In Vivo Response to Meshes Implanted in Rabbits. J Urol. 2016;196(1):261–9; doi: 10.1016/j.juro.2016.02.067, **IF 4.47**
- Darzi S, Urbankova I, Su K, White J, Lo C, Werkmeister JA, Gargett CE, Deprest J, Alexander D. Tissue response to collagen containing polypropylene meshes in an ovine vaginal repair model. Acta Biomater. 2016 Jul 15 15;39: 114/123; doi: 10.1012/j.actbio.2016.05.010, **IF 6.02**
- Krofta L, Havelková L, Urbánková I, Krčmář M, Hynčík L, Feyerreisl J, Finite element model focused on stress distribution in the levator ani muscle during vaginal delivery, Int. Urogynecol J, 2017 Feb;(28)2:275-284.; doi: 10.1007/.00192-016-3126-1; **IF 1.96**
- Hympanova L, Mori da Cunha MGMC, Rynkevic R, Zündel M, Gallego MR, Vange J, Callewaert G, Urbankova I, Van der Aa F, Mazza E, Deprest J., Physiologic musculofascial compliance following reinforcement with electronspun polycaprolactone-ureidopyrimidinone mesh in rat model. J Mech Behav Biomed Mater 2017, Jun 27(74), 349 – 357; doi:10.1016/j.jmbbm.2017.06.032, **IF 1.96**