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Animal Models of Double Incontinence: “Fecal and Urinary”

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Abstract

Throughout the world, animal models are being used as simulators of human anatomy and pathophysiology with most of the investigations and treatments first tested on them. Double incontinence (DI) includes both urinary and anal incontinence. This chapter is focused on the use of animals as models to understand pathogenesis, diagnosis and management of double incontinence (DI). DI is a complex disease with variant prevalence around the world which has a severe impact on quality of life (QoL). Many studies are designed to employ rodent and rabbit models to understand the pathogenesis of urinary and fecal incontinence. Urodynamic studies including leak point pressure (LPP) and urethral pressure profilometry (UPP) are used in establishing diagnosis of stress urinary incontinence. Rats have also been used to study fecal incontinence using neurophysiological and sacral nerve stimulation tests. The surgical treatment of double incontinence involves use of mesh, which was initially tested on animals. Animal models have also been used to train surgeons for perineal tear repair surgery. We conclude that the use of animal models provides best approach to learn these specialized surgical skills for medical practitioners and researchers.

Keywords: animal model, double incontinence, stress incontinence, fecal incontinence, human

1. Introduction

The prevalence of female urinary incontinence (UI) in Europe ranges from 14.1 to 68.8% and increases with age [1]. Specifically, stress urinary incontinence (SUI) is highest among all types of UI and is estimated at 23.7% [2]. The prevalence of fecal incontinence (FI) ranges from 2.2 to 50% in women with urinary incontinence or pelvic organ prolapse [3]. FI and UI are pelvic floor disorders (PFD) which lead to social embarrassment and have poor impact

on quality of life. Over \$12 billion are spent annually for management of SUI in women [4]. The average annual total cost for fecal incontinence is estimated at \$4110 per person [5]. Stress urinary incontinence (SUI) may be defined as involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing. Urgency urinary incontinence (UUI) relates to involuntary loss of urine associated with a desire to void, while anorectal incontinence (AI) is a complaint of involuntary loss of feces or flatus.

The ultimate success of long-term management for double incontinence (DI) is based on an understanding of disease pathophysiology. Little is known about the degree to which UI and FI share risk factors. Animal models have been used to understand pathogenesis of these conditions in humans and for developing novel treatment alternatives. Even though many animal models have been developed to understand pathogenesis, yet many of etiological factors are not explained. Many animal models are used as simulators for teaching surgical skills but long-term studies have not shown the desired improvement in surgical outcome [6]. The surgical procedures in humans were developed through the use and application of animal model as slings and trocar-driven implants [7] for anti-incontinence procedures.

Urinary incontinence is relatively easy to understand when compared to fecal incontinence as anal sphincter defects and FI are complicated surgical problems. Research on use of stem cell for treatment of FI was conducted on rabbits by an iatrogenic sphincter defect, created by cutting of anal sphincter. Human umbilical cord matrix (hUCM) and stem cells from rabbit femur and tibia were harvested and transplanted into injured sphincters which later showed an improvement in their function. Bone marrow-derived stem cells and mesenchymal cells of animals have shown to enhance contractile function of anal sphincter without surgical repair [8]. The limitation of using animals is in their difference with anatomy and size of viscera, which affects the functional outcome. Human cadavers have been used for a long time for teaching anatomy, but due to ethical issues animals were introduced in medical teaching. Animal models were found quite effective, but because of major difference in functional anatomy, mannequins were introduced for medical teaching and learning. There are many centers for simulation-based innovation for medical education (SIME), which probably would give similar results [9].

Most of the studies on new medical and surgical treatment involve the use of animal models for preclinical trials. In this chapter, we discussed use of animal models for relevant research, procedures on pathogenesis and surgical training techniques for DI. We have used standardized terminology for definitions as described by the International Continence Society (ICS) and International Urogynecological Association (IUGA) joint report on terminology [10, 11].

2. Methods of determining SUI in animal models

SUI is a clinical diagnosis mainly by history and physical examination. ICS has defined urodynamic stress incontinence as involuntary leakage of urine during filling cystometry, associated with increased intra-abdominal pressure, in the absence of a detrusor contraction

[10]. The role of urodynamic studies (UDS) is important in identifying types of SUI. Types of SUI can be determined with valsalva leak point pressure (VLPP) and urethral pressure profilometry (UPP). According to Blaivis, SUI types 1 and 2 are related to urethral hypermobility with VLPP > 90 cm of water for type 1 and between 60 and 90 cm of water for type 2, respectively. Blaivis type 3 SUI is with VLPP < 60 cm water, also known as intrinsic sphincter deficiency (ISD). In addition, a urethral pressure profile (UPP which is urethral pressure–detrusor pressure) < 20 cm water is also seen in the cases of ISD [12]. Animal models that simulate SUI provide an assessment of the mechanism of risk factors, including childbirth injuries, preclinical testing of new treatments and therapies for SUI. Since animals cannot express intent, the use of these animal models has been focused on measuring decreased urethral resistance [13].

2.1. Sneeze testing

SUI is clinically assessed on humans as observation of involuntary leakage from the urethra with effort or physical exertion, or on sneezing or coughing [10]. Based on the urinary leak with a rise in abdominal pressure, sneeze test can be performed in female rat under anesthesia. A whisker cut from anesthetized rat was used to tickle its nose. Even under anesthesia the rat responded with a small sneeze, which transiently increased abdominal pressure. Karl et al. performed cystometry with methylene blue dye in bladder to detect urinary leak. The animal was diagnosed as incontinent if they leaked during the sneeze test and continent if no leak on sneezing was observed [13, 14].

2.2. LPP testing

The human bladder functions by storage and voiding of urine. Voiding is accompanied by an increase in detrusor pressure and a decrease in urethral pressure. In leak point pressure (LPP) testing [15], rats were anesthetized and a transperitoneal catheter implanted in the bladder dome was tunneled subcutaneously from the back of the bladder neck to an exit via the skin. The catheter was capped and the skin incision closed in two layers. The bladder catheter was connected to both a syringe pump and a pressure transducer. The bladder when filled with room-temperature saline through the catheter, the bladder pressure was recorded via a microtip transducer urethral catheter. Pressure and force transducer signals were amplified and recorded on a chart recorder. All bladder pressures were referenced to air pressure at the level of the bladder very similar to LPP assessment in humans with use of external transducers. The three commonly used mechanisms are manual pressure/Crede's LPP, electrical stimulation LPP and table tilt LPP [16–18].

2.2.1. Manual LPP testing

To perform manual LPP testing in rats, they put supine on table and a passive/manual abdominal pressure is applied and increased gradually, thus increasing the vesical pressure until leakage is observed at the urethral meatus. The peak bladder pressure was taken as the LPP. After leak, the external pressure is rapidly removed and bladder pressure quickly returns to baseline [17].

2.2.2. Vertical tilt table LPP

Rat is mounted on a vertical tilt table to keep the bladder erect during UDS, similar to human studies. A saline reservoir is connected to a suprapubic catheter to passively increase bladder pressure by elevating it and maintaining it at a range of pressures (20, 40 and 60 cm H₂O) [19]. In this method, the spinal cord is often transected usually at T8–T9. This transaction eliminates the supraspinal reflex voiding but preserves the urethral reflexes induced by bladder distention, which are predominantly organized in the lumbosacral spinal cord [20]. Studies have shown comparable results of LPP with sneeze test, manual pressure test and vertical tilt table test [21].

2.2.3. Electrical stimulation LPP testing

Electrical stimulation of abdominal muscles for 1 s induces sudden increase in both the intra-abdominal and the intravesical pressure. The lowest intravesical pressure that induced fluid leakage from the urethral orifice (leak point pressure) and the maximal intravesical pressure without urine leakage were recorded and were used to evaluate urethral resistance. However, like tilt table testing, electrical stimulation LPP testing also requires spinal cord transection, suppressing supraspinal continence control [22].

2.3. Urethral closure pressure testing

Effects of stem cell transplantation in rats were evaluated through urodynamic testing, and morphologic changes of the urethra and surrounding tissues were studied [23] both before and after transplantation. The bladder catheter was used as an intraurethral pressure measurement catheter, connecting it to a three-limb tube through a conversion joint. One end of that three-limb tube was connected to the intraurethral pressure sensor, and the other end was connected to the micropump, maintaining the original intraurethral pressure measurement catheter. Pressure was set at 0, and infusion by micropump at rate of 0.25 ml/min was started. Urethral pressure profilometry (UPP) rod was used to pull the intraurethral pressure measurement catheter at 0.1 mm/s traction speed. Meanwhile, intraurethral pressure and intrabladder pressure were recorded. Maximum urethral closure pressure (MUCP) was intraurethral pressure minus intrabladder pressure. Functional urethra length (FUL) was also calculated. Transplantation of adipose-derived stem cells significantly strengthened local urethral muscle layers and significantly improved the morphology and function of sphincters.

3. Establishing the causes of incontinence in animals

3.1. Causes of SUI

The childbirth injury leads to SUI due to musculofascial and neurovascular damage causing weakness in pelvic floor support [24]. Rodents are used to establish the vaginal injury as a leading cause of SUI which occur secondary to vaginal dilatation (VD) during childbirth in human.

Several studies [25, 26] have demonstrated vaginal injury by VD which is induced by using a Foley catheter with cut tip and inflated with different fluid volumes from 2 to 4 ml. This creates pressure in vagina and iatrogenic injury to the urethra, bladder, vagina and levator muscles. Functionally, VD results in decreased urethral resistance, as evidenced by lowered leak point pressures on urodynamic testing done in most of the VD studies [27]. In a study by Lin et al., VD was created in mice by 0.1–0.3 ml balloon in comparison with sham distension. LPP was significantly lower in groups after VD with 0.2–0.3 ml as compared to sham [28]. Research has shown that this procedure has helped in understanding molecular factors like chemokines, neuro-regenerative agents and pharmacological agents that contribute to functional recovery including stem cell mobilization following injury [27, 29]. It has also helped in evaluation of the impact of contributing/decompensating factors in the pathophysiology and recovery of continence.

3.2. Causes of UUI

Urinary urge incontinence is observed among patient of overactive bladder (OAB) which is called wet OAB. There are many pathophysiological bases for its explanation including neuro-genic and myogenic theories. It has been established through animal studies that urge incontinence is predominantly due to a defect in bladder muscle [30]. In a study on pigs, unstable bladder contractions were produced against induced outflow obstruction, bladder distention and bladder transaction. In affected pigs, stimulation of the spinal roots could no longer alter detrusor contraction. Similarly, sectioning of the spinal roots in these animals did not eliminate the unstable pressure rise explaining myogenic basis of OAB [31]. These manipulations do not eliminate the possibility of increased neuronal firing at the ganglionic level. However, recently, it has been shown that both hexamethonium (which blocks ganglionic transmission) and tetrodotoxin (TTX, which abolishes all neuronal activity) inhibit micturition but do not abolish unstable contractions in the pigs or rats [32, 33], hence supporting myogenic theory. The majority of the structural changes seen were obtained with light microscopic techniques, and local detrusor changes were found similar to those among human with OAB.

3.3. Causes of DI

The innervation of the external urethral sphincter (EUS) from the pudendal nerve is similar between rats and humans [34]. In female rats, the motor pudendal nerve bifurcates within Alcock's canal into separate fascicles that innervate the external anal sphincter (EAS) and EUS. The pudendal nerve controls EUS activity, including tonic activity during continence, and activates to strengthen the guarding response to prevent urinary leakage [35]. It can be trapped and injured during vaginal childbirth because it passes through Alcock's canal in the ischio-rectal fossa, especially between the sacrospinous and the sacrotuberous ligaments [36]. Pudendal nerve crush (PNC) injury was induced in rats simulating childbirth injury, leading to deficiency of EUS and causing SUI [37]. Another rat study demonstrated the Pudendal nerve injury effects on external anal sphincter similar to injury during child birth in human affecting EAS and causing FI. In Healy et al.'s study [38], one group of rats used for the experiment had induced bilateral inferior rectal nerve crush (Group A) injury which then acted as a positive control and was observed for EAS effects. In another group (Group B), an intrapelvic retro-uterine balloon

inflation was performed, mimicking the pressure effects of child birth on the pelvic side wall and pelvic floor. Both groups of rats showed signs of EAS muscle atrophy and denervation, leading to FI. However, EMG signs of re-innervation were seen in both groups and recovery of muscle mass at 4 weeks, mimicking human pathophysiology of fecal incontinence.

4. Use of animal model in conservative treatment of incontinence

Since conservative management involves the use of medicine with many side effects, laboratory animals are used in preclinical drug trials. Several animal models have been used to evaluate the best possible conservative remedies for treating both urinary and fecal incontinence. Animal models were used to test midurethral slings for surgical treatment of SUI which currently provides the best surgical cure. An outline of conservative management of double incontinence is shown in **Figure 1**.

4.1. Conservative management of SUI

Conservative treatment of SUI includes lifestyle interventions, pelvic floor muscle training, electrical stimulation, vaginal cones, urethral plugs and the drug duloxetine. Medical treatment has been tried and tested on animal models to assess their safety and effects on nervous system in improving SUI.

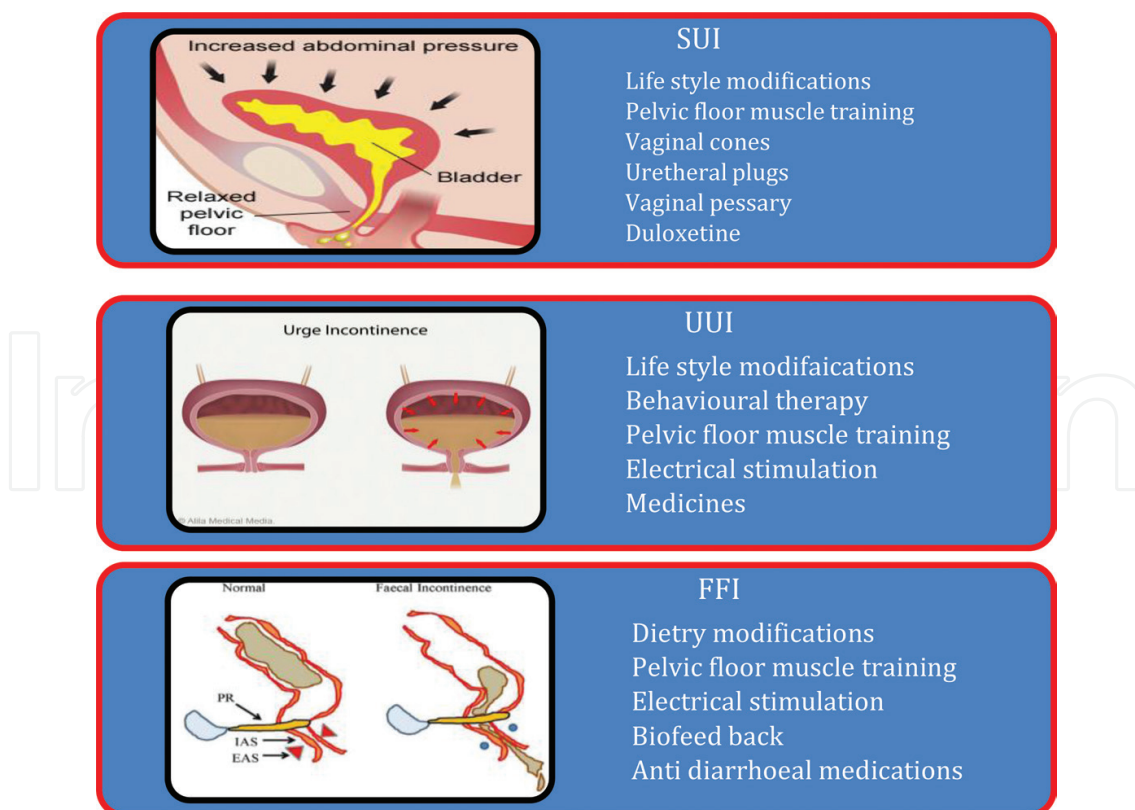


Figure 1. Conservative management of double incontinence.

4.1.1. Selective norepinephrine reuptake inhibitor

Venlafaxine is a selective norepinephrine (NE) reuptake inhibitor, and it significantly decreases the contraction of bladder muscle and increases urethral resistance. This was initially tested on rabbits and rodents. Bladder and proximal urethral muscle strips were electrically stimulated, and their contractile responses were measured both pre- and posttreatment with venlafaxine. It was observed that it significantly increased the contraction of urethral strips ($P = 0.008$) tested by urethral pressure profilometry (UPP) [39].

4.1.2. Norepinephrine (NE) and serotonin (5-HT) reuptake inhibitor

Duloxetine, a norepinephrine (NE) and serotonin (5-HT) reuptake inhibitor, can prevent SUI by facilitating noradrenergic and serotonergic systems in the spinal cord at S3 level (nucleus of Onuf) to enhance the sneeze-induced active urethral closure mechanism. Based on this mechanism, duloxetine is currently being used in humans for conservative management of SUI. Before the human trials, it was tested on cat sphincter [40] and in rat models. Duloxetine caused urethral closing contractions and increased the urethral resistance (leak point pressure) measured using a microtip transducer catheter in the middle urethra of rat models [41].

4.1.3. Stem cell therapy

One of the SUI causes includes urethral sphincter deficiency which is called type III SUI or intrinsic sphincter deficiency (ISD). This occurs usually due to inherent defects in the collagen and elastin of urethral sphincter. Many preclinical trials have investigated whether transplantation of patient's own skeletal muscle-derived cells (SkMDCs) can restore the sphincter musculature. The specific cell type of SkMDCs is myoblasts, satellite cells, muscle progenitor cells, or muscle-derived stem cells. The other stem cell (SC) types used for urethral defects include those from the bone marrow, umbilical cord blood and adipose tissue. These cells are injected as periurethral injections. Herrera-Imbroda et al. used rat models for SC injection, and rats were assessed by LPP testing for therapeutic efficacy of SC treatment [42]. The study also used histological assessment, which revealed the sphincter muscle content, existence of transplanted SCs and possible differentiation of these SCs.

Rodents were also used to explore the feasibility, safety and efficacy of cellular regimen to treat SUI. SUI was induced by vaginal dilatation (VD), and cystoscopic urethral injections of bone marrow or adipose tissue-derived mesenchymal stromal cells (BMSC/ADSC) were given to rats. It was observed that MSCs restored the continence mechanism by improving vascular and connective tissue status of urethral tissues after VD [43]. In another study, human mesenchymal stromal cells were isolated, expanded and characterized. These cells were injected trans-urethrally in immune-suppressed Göttingen Minipigs. The study found this cellular sphincter therapy in Göttingen Minipigs as very safe and effective against SUI [44]. Some animal studies employed dogs with induced SUI and injected SCs therapy to test safety and efficacy for SUI treatment and found similar results [45].

4.2. Conservative treatment of UUI

Clinical observations as well as results from recent studies on murine showed that iatrogenic bladder outlet obstruction leads to a rise in detrusor pressure, mimicking leak in humans secondary to detrusor overactivity (DO) in cases of UUI. Murines were induced DO and then treated by the use of botulinum toxin A (BoNT-A). The therapeutic effects of intramural injections of botulinum toxin A (BoNT-A) into the bladder wall resulted in suppression of detrusor overactivity in murine as seen in human bladder, and the refractory cases of UUI secondary to DO have shown same results with botulinum toxin A (BoNT-A) [46].

4.3. Conservative treatment of FI

Modifying irregular bowel habits is often the first step to manage FI. Pelvic floor exercises with and without biofeedback therapy, reusable bodyworn products and antidiarrheal treatment all play some role in treatment of FI. Sacral nerve stimulation (SNS) and stem cell therapy for improving contractile function of anal sphincter have been studied on animal models.

4.3.1. Sacral nerve stimulation (SNS) therapy

Fecal incontinence is multifactorial in origin. Most of the human studies have focused on anal sphincter functions and its restoration for treatment of FI. There have been numerous animal studies which investigated direct effects of SNS on the muscles of continence. In one study, ten dogs received electrical stimulation of the sacral plexus. Histochemical analysis of the striated external anal sphincter following chronic electrical stimulation demonstrated hypertrophy of stimulated muscle fibers. However, these changes reverted to pre-stimulation level 3 months after the stimulation. Anal tone and reflexes were measured before and during acute stimulation and demonstrated that SNS did not have any significant effect on internal anal sphincter or external anal sphincter force, the recto-anal inhibitory or recto-anal excitatory reflexes, internal anal sphincter slow wave frequency or wave amplitude [47]. The mechanism of action of SNS with the use of surgically implanted interstim is not very clear; however, it was found to be very effective in patients with FI [48].

4.3.2. Stem cell therapy

Stem cell injection at the site of injury can enhance contractile function of the anal sphincter without surgical repair. Human umbilical cord matrix (hUCM) cells have been described as having the characteristics of myofibroblasts, which play a role in healing by producing a wide range of cytokines, growth factors, chemokines and inflammatory mediators. Rabbit bone marrow (rBM) cells are known to secrete many growth factors which contribute to cell propagation and differentiation. Harvested hUCM and rBM stem cells from rabbit femurs and tibias were injected in surgically incised external anal sphincter of the white New Zealand rabbits. Electromyography showed significant improvement in sphincter function 2 weeks after local injection of rBM stem cells, and histopathologic evaluation showed normal

or muscle-dominant sphincter structure in all animals receiving rBM and fibrous-dominant sphincter structure in most animals receiving hUCM cells [8].

5. The role of animal studies in surgical management of DI

5.1. Surgical treatment of SUI

There are a variety of surgical treatment options for SUI. The two most effective procedures are Burch colposuspension and midurethral slings (MUS), which are available in different synthetic material. Each material has been tested for its efficacy and safety. There are many animal studies regarding the use of mesh before its use in human.

5.1.1. Efficacy of slings tested by LPP

Surgical management including the suburethral sling is one of the most common treatment options for SUI, with an overall objective cure rate of 82% [49]. Suburethral sling therapy provides stability to the supporting layer under the urethra and helps in leak of urine against the rise in abdominal pressure. The urethra remains compressed against the suburethral sling, and continence is maintained. While a sling procedure offers the highest success rate, it also results in the highest morbidity and complication rate among all anti-incontinence procedures. In the last several years, a number of modifications to the sling procedure have been proposed to improve its safety and efficacy while decreasing morbidity. SUI in rats was induced by pudendal nerve transaction (PNT), they were treated by polypropylene suburethral sling and the efficacy of sling was assessed by an increase in LPP [50].

5.1.2. Tissue reaction of different sling materials

Tension-free vaginal tape (TVT) with polypropylene was first introduced by Ulmsten for surgical treatment of SUI and has shown good success rate [51]. The tensile properties of polypropylene used in TVT were studied in rats and found to be significantly greater than cadaveric fascia lata [52]. There have been many other sling procedures using same material with different surgical approaches. Another study on white rabbits has evaluated tissue reactions to five sling materials used in five different procedures like tension-free vaginal tape (TVT), intravaginal slingplasty (IVS) for SUI surgery and polypropylene mesh for hernia repair. The other two procedures to cure SUI included suprapubic approach using suburethral polypropylene tape and cadaveric fascia lata. Rabbit abdominal skin was incised, and a patch of all five sling material was attached with absorbable suture. Study compared the mesh-to-tissue attachment strength of four sling mesh materials on days 2, 7, 15 and 30 after implantation by electron microscopic studies. All five synthetic sling materials produced similar tissue reactions beginning soon after implantation. Cadaveric fascia lata persisted in tissue with remarkable perifascial fibrosis at day 30. When comparing the four polypropylene mesh materials, the attachment capacity of TVT was superior and that of IVS was the least of the four. TVT was statistically better than IVS at all data points. Suprapubic approach with polypropylene and hernia mesh provided results similar to those of TVT [53].

5.2. Surgical treatment of FI

Obstetric anal sphincter trauma is the most common cause of fecal incontinence with a severe impact on quality of life. Anal sphincter rupture is reported in about 2.5% of vaginal deliveries in centers that practice mediolateral episiotomy and about 11% in centers that practice mid-line episiotomy [54]. The effect of anal sphincter laceration (with repair) at the time of parturition after term pregnancy on physiologic function of the external anal sphincter was studied on eighty rats [55]. Overall, anal sphincter laceration at time of delivery results in significantly impaired anal function. Rat anal sphincter neurophysiologic functions were assessed. Recovery of sphincter function was evident as early as three months and maintained at six months after injury. The diagnosis and repair of sphincter tear is very important. Unrepaired or badly repaired sphincter can lead to FI. Several simulator models have been developed to provide surgical training to consultants, midwives and trainees. The early diagnosis of anal sphincter injury is very important for effective surgical outcome. The pig model was introduced due to its similarity to both internal and external anal sphincters [56]. The model used cadaveric pig perineum with a clear demarcation between internal and external anal sphincters simulating human sphincters. Another study showed effective teaching of repair of perineal tears using goat perineum model (**Figure 2**), which mimics human female anatomy [57]. Both anal sphincter latex/plastic and cadaveric animal sphincter models have been effectively used for hands on training in different workshops.

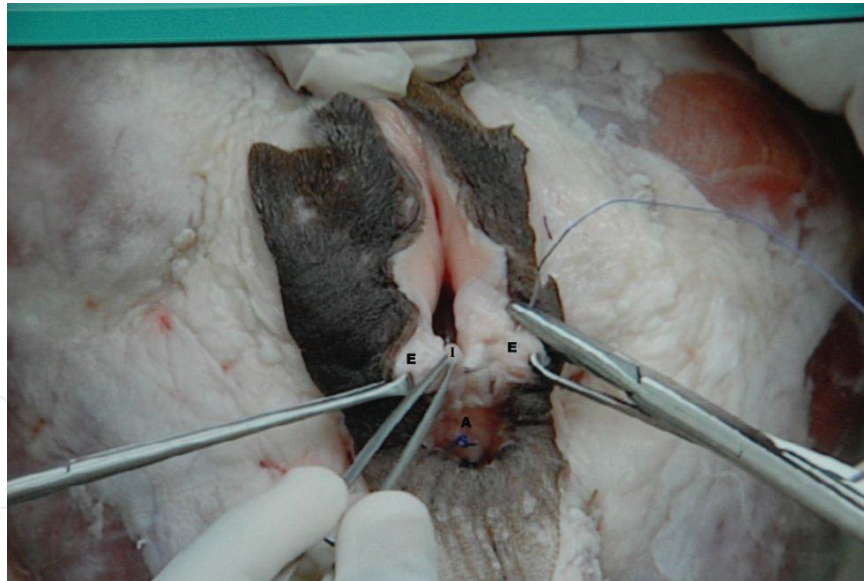


Figure 2. Multiparous goat. Cut edge of external anal sphincter (E) held by Allis forceps, (I) internal anal sphincter between anal canal (A) and (E) external anal sphincter.

5.2.1. Artificial anal sphincter

The artificial anal sphincter is used in cases where other treatment modalities fail. It includes an inflatable expander that compresses and flattens the bowel against a pillow. Before its

experiment on humans, it was tried in 16 animals. In experimental animals, anal sphincters were destroyed and artificial sphincter device was implanted. The animals were observed for twenty weeks. The study concluded the safety of implanted sphincter against anal ischemia. Moreover, animals were continent during 85% of activation times [58].

6. Animal genetic models developed for incontinence/SUI studies

During last decade, investigators have developed and tested animal models of SUI in the female rat, seeking to mimic the symptoms of SUI in female patients. Bilateral pudendal nerve crush injury or transection or sciatic nerve transection has been used to cause SUI in rats. The VD model was used by Lin et al. [28] to simulate the damage that occurs in the pelvic floor during vaginal delivery of children. They demonstrated the feasibility of creating a mouse model of acute SUI by VD. Distention volumes of 0.1–0.3 ml in 20 g female mice of strain C57BL/6 resulted in significant reductions of LP, possibly due to partial urethral denervation. This novel model of SUI in mice could be used in future mechanistic studies of female SUI treatment. The childbirth induced vaginal distension, and SUI can be correlated but women recover out of these transient changes with only few remaining symptomatic for SUI. There is a need to develop specific mouse genetic models for incontinence/SUI induced by VD. Further studies can be performed to know the spontaneous cure of incontinence.

7. Conclusion

The use of animal models has helped in understanding the pathogenesis and etiology of both urinary and fecal incontinence. Due to ethical issues related to human cadaveric studies, animal models are good substitute for research related to surgical innovations for treatment of double incontinence. Animal models like sheep, goat and pig have been validated for surgical training for perineal tears. The latest use of animal model is related to studies on mouse for simulated birth trauma-induced SUI and stem cell treatment for double incontinence.

List of abbreviations and acronyms

DI	Double incontinence
FI	Fecal incontinence
UI	Urinary incontinence
SUI	Stress urinary incontinence
UUI	Urgency urinary incontinence
OAB	Overactive bladder

LPP	Leak point pressure
UPP	Urethral pressure profilometry
UDS	Urodynamic studies
VLPP	Valsalva leak point pressure
ISD	Intrinsic sphincter deficiency
PFDD	Pelvic floor dysfunction
ICS	International Continence Society
IUGA	International Urogynecological Association
VD	Vaginal dilatation
PNC	Pudendal nerve crush
NE	Norepinephrine
EUS	External urethral sphincter
EAS	External anal sphincter
TTX	Tetrodotoxin
SC	Stem cells
SkMDCs	Skeletal muscle-derived cells
SNS	Sacral nerve stimulation
hUCM	Human umbilical cord matrix
rBM	Rabbit bone marrow
BoNT-A	Botulinum toxin A
PNT	Pudendal nerve transaction
TVT	Tension-free vaginal tape
IVS	Intravaginal slingplasty
BMSC	Bone marrow-derived stem cells
ADSC	Adipose tissue-derived mesenchymal stromal cells

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References

- [1] Cerruto MA, D'Elia C, Aloisi A, Fabrello M, Artibani W. Prevalence, incidence and obstetric factors' impact on female urinary incontinence in Europe: A systematic review. *Urologia Internationalis*. 2012;**90**(1):1-9
- [2] Minassian VA, Stewart WF, Wood GC. Urinary incontinence in women: Variation in prevalence estimates and risk factors. *Obstetrics & Gynecology*. 2008;**111**(2, Part 1):324-331
- [3] Devesa JM. Fecal incontinence: Major problem or incidental finding? *Techniques in Coloproctology*. 2016;**20**(2):77-79
- [4] Chong EC, Khan AA, Anger JT. The financial burden of stress urinary incontinence among women in the United States. *Current Urology Reports*. 2011;**12**(5):358-362
- [5] Xu X, Menees SB, Zochowski MK, Fenner DE. Economic cost of fecal incontinence. *Diseases of the Colon & Rectum*. 2012;**55**(5):586-598
- [6] Powell CR. Conditional electrical stimulation in animal and human models for neurogenic bladder: Working toward a neuroprosthesis. *Current Bladder Dysfunction Reports*. 2016;**11**(4):379-385
- [7] Fokaefs ED, Lampel A, Hohenfellner M, Lazica M, Thuroff JW. Experimental evaluation of free versus pedicled fascial flaps for sling surgery of urinary stress incontinence. *The Journal of Urology*. 1997;**157**(3):1039-1043
- [8] Aghaee-Afshar M, Rezazadehkermani M, Asadi A, Malekpour-Afshar R, Shahesmaeili A, Nematollahi-Mahani SN. Potential of human umbilical cord matrix and rabbit bone marrow-derived mesenchymal stem cells in repair of surgically incised rabbit external anal sphincter. *Diseases of the Colon & Rectum*. 2009;**52**(10):1753-1761
- [9] Okuda Y, Bryson EO, DeMaria S, Jacobson L, Quinones J, Shen B, Levine AI. The utility of simulation in medical education: What is the evidence? *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine*. 2009;**76**(4):330-343
- [10] Haylen BT, De Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, Monga A, Petri E, Rizk DE, Sand PK, Schaer GN. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *International Urogynecology Journal*. 2010;**21**(1):5-26
- [11] Sultan AH, Monga A, Lee J, Emmanuel A, Norton C, Santoro G, Hull T, Berghmans B, Brody S, Haylen BT. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female anorectal dysfunction. *Neurourology and urodynamics*. 2017 Jan 1;**36**(1):10-34.
- [12] Housley SL, Harding C, Pickard R. Urodynamic assessment of urinary incontinence. *Indian Journal of Urology*. 2010;**26**(2):215

- [13] Jiang HH, Damaser MS. Animal models of stress urinary incontinence. In: *Urinary Tract*. Berlin, Heidelberg: Springer; 2011. pp. 45-67
- [14] Lin AS, Carrier S, Morgan DM, Lue TF. Effect of simulated birth trauma on the urinary continence mechanism in the rat. *Urology*. 1998;**52**(1):143-151
- [15] Sievert KD, Bakircioglu ME, Tsai T, Dahms SE, Nunes L, Lue TF. The effect of simulated birth trauma and/or ovariectomy on rodent continence mechanism. Part I: Functional and structural change. *The Journal of Urology*. 2001;**166**(1):311
- [16] Kefer JC, Liu G, Daneshgari F. Pubo-urethral ligament transection causes stress urinary incontinence in the female rat: A novel animal model of stress urinary incontinence. *The Journal of Urology*. 2008;**179**(2):775-778
- [17] Cannon TW, Wojcik EM, Ferguson CL, Saraga S, Thomas C, Damaser MS. Effects of vaginal distension on urethral anatomy and function. *BJU International*. 2002;**90**(4):403-407
- [18] Lee JY, Cannon TW, Pruchnic R, Fraser MO, Huard J, Chancellor MB. The effects of peri-urethral muscle-derived stem cell injection on leak point pressure in a rat model of stress urinary incontinence. *International Urogynecology Journal*. 2003;**14**(1):31-37
- [19] Kamo I, Cannon TW, Conway DA, Torimoto K, Chancellor MB, de Groat WC, Yoshimura N. The role of bladder-to-urethral reflexes in urinary continence mechanisms in rats. *American Journal of Physiology – Renal Physiology*. 2004;**287**(3):F434-F441
- [20] Cannon TW, Lee JY, Somogyi G, et al. Improved sphincter contractility after allogenic muscle-derived progenitor cell injection into the denervated rat urethra. *Urology*. 2003;**62**:958-963
- [21] Conway DA, Kamo I, Yoshimura N, Chancellor MB, Cannon TW. Comparison of leak point pressure methods in an animal model of stress urinary incontinence. *International Urogynecology Journal*. 2005;**16**(5):359-363
- [22] Kamo I, Hashimoto T. Involvement of reflex urethral closure mechanisms in urethral resistance under momentary stress condition induced by electrical stimulation of rat abdomen. *American Journal of Physiology – Renal Physiology*. 2007;**293**(3):F920-F926
- [23] Wu G, Song Y, Zheng X, Jiang Z. Adipose-derived stromal cell transplantation for treatment of stress urinary incontinence. *Tissue and Cell*. 2011;**43**(4):246-253
- [24] Allen RE, Hosker GL, Smith AR, Warrell DW. Pelvic floor damage and childbirth: A neurophysiological study. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1990;**97**(9):770-779
- [25] Hijaz A, Daneshgari F, Sievert KD, Damaser MS. Animal models of female stress urinary incontinence. *The Journal of Urology*. 2008;**179**(6):2103-2110
- [26] Damaser MS, Broxton-King C, Ferguson C, Kim FJ, Kerns JM. Functional and neuro-anatomical effects of vaginal distention and pudendal nerve crush in the female rat. *The Journal of Urology*. 2003;**170**(3):1027-1031

- [27] Pan HQ, Kerns JM, Lin DL, Liu S, Esparza N, Damaser MS. Increased duration of simulated childbirth injuries results in increased time to recovery. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology*. 2007;**292**(4):R1738-R1744
- [28] Lin YH, Liu G, Daneshgari F. A mouse model of simulated birth trauma induced stress urinary incontinence. *Neurourology and Urodynamics*. 2008;**27**(4):353-358
- [29] Woo LL, Hijaz A, Kuang M, Penn MS, Damaser MS, Rackley RR. Over expression of stem cell homing cytokines in urogenital organs following vaginal distention. *The Journal of Urology*. 2007;**177**(4):1568-1572
- [30] Brading AF. A myogenic basis for the overactive bladder. *Urology*. 1997;**50**(6):57-67
- [31] Hailemariam S, Elbadawi A, Yalla SV, Resnick NM. Structural basis of geriatric voiding dysfunction. V. Standardized protocols for routine ultrastructural study and diagnosis of endoscopic detrusor biopsies. *The Journal of Urology*. 1997;**157**:1783-1801
- [32] Turner WH. An experimental urodynamic model of lower urinary tract function and dysfunction [DM thesis]. Cambridge, England: Cambridge University; 1997
- [33] Igawa Y, Mattiasson A, Andersson K-E. Micturition and premicturition contractions in unanesthetized rats with bladder outlet obstruction. *The Journal of Urology*. 1994;**151**:244-249
- [34] McKenna KE, Nadelhaft I. The organization of the pudendal nerve in the male and female rat. *Journal of Comparative Neurology*. 1986;**248**(4):532-549
- [35] Park JM, Bloom DA, McGuire EJ. The guarding reflex revisited. *British Journal of Urology*. 1997;**80**(6):940-945
- [36] Snooks SJ, Swash M, Henry MM, Setchell M. Risk factors in childbirth causing damage to the pelvic floor innervation. *International Journal of Colorectal Disease*. 1986;**1**(1):20-24
- [37] Kerns JM, Damaser MS, Kane JM, Sakamoto K, Benson JT, Shott S, et al. Effects of pudendal nerve injury in the female rat. *Neurourology and Urodynamics*. 2000;**19**(1):53-69
- [38] Healy CF, O'Herlihy C, O'Brien C, O'Connell PR, Jones JF. Experimental models of neuropathic fecal incontinence: An animal model of childbirth injury to the pudendal nerve and external anal sphincter. *Diseases of the Colon & Rectum*. 2008;**51**(11):1619-1626
- [39] Bae JH, Moon DG, Lee JG. The effects of a selective noradrenaline reuptake inhibitor on the urethra: An in vitro and in vivo study. *BJU International*. 200;**88**(7):771-775
- [40] Thor KB, Katofiasc MA. Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized female cat. *Journal of Pharmacology and Experimental Therapeutics*. 1995;**274**(2):1014-1024
- [41] Miyazato M, Kaiho Y, Kamo I, Chancellor MB, Sugaya K, de Groat WC, Yoshimura N. Effect of duloxetine, a norepinephrine and serotonin reuptake inhibitor, on sneeze-induced urethral continence reflex in rats. *American Journal of Physiology – Renal Physiology*. 2008;**295**(1):F264-F271

- [42] Herrera-Imbroda B, Lara MF, Izeta A, Sievert KD, Hart ML. Stress urinary incontinence animal models as a tool to study cell-based regenerative therapies targeting the urethral sphincter. *Advanced Drug Delivery Reviews*. 2015;**82**:106-116
- [43] Sadeghi Z, Isariyawongse J, Kavran M, Izgi K, Marini G, Molter J, Daneshgari F, Flask CA, Caplan A, Hijaz A. Mesenchymal stem cell therapy in a rat model of birth-trauma injury: Functional improvements and biodistribution. *International Urogynecology Journal*. 2016;**27**(2):291-300
- [44] Amend B, Kelp A, Vaegler M, Klünder M, Frajs V, Klein G, Sievert KD, Sawodny O, Stenzl A, Aicher WK. Precise injection of human mesenchymal stromal cells in the urethral sphincter complex of Göttingen Minipigs without unspecific bulking effects. *Neurourology and Urodynamics*. 2016;**99**:1-11
- [45] Williams JK, Eckman D, Dean A, Moradi M, Allickson J, Cline JM, Yoo JJ, Atala A. The Dose-Effect Safety Profile of Skeletal Muscle Precursor Cell Therapy in a Dog Model of Intrinsic Urinary Sphincter Deficiency. *Stem cells translational medicine*. 2015 Mar 1; **4**(3):286-94
- [46] Krhut J, Zvara P. Intravesical instillation of botulinum toxin A: An in vivo murine study and pilot clinical trial. *International Urology and Nephrology*. 2011;**43**(2):337-343
- [47] Carrington EV, Evers J, Grossi U, Dinning PG, Scott SM, O'Connell PR, Jones JF, Knowles CH. A systematic review of sacral nerve stimulation mechanisms in the treatment of fecal incontinence and constipation. *Neurogastroenterology & Motility*. 2014;**26**(9):1222-1237
- [48] Indinnimeo M, Moschella CM, Bernardi G, Gozzo P. Sacral nerve stimulation in fecal incontinence. In: *Management of Fecal Incontinence*. Springer International Publishing; USA 2016. pp. 75-90
- [49] Leach GE, Dmochowski RR, Appell RA, et al. Female Stress Urinary Incontinence Clinical Guidelines Panel summary report on surgical management of female stress urinary incontinence. *The Journal of Urology*. 1997;**158**:875-880
- [50] Hijaz A, Bena J, Daneshgari F. Long-term efficacy of a vaginal sling procedure in a rat model of stress urinary incontinence. *The Journal of Urology*. 2005;**173**(5):1817-1819
- [51] Ulmsten U. Intravaginal slingplasty (IVS): An ambulatory surgical procedure for treatment of urinary incontinence. *Scandinavian Journal of Urology and Nephrology*. 1995;**29**:75-82
- [52] Spiess PE, Rabah D, Herrera C, Singh G, Moore R, Corcos J. The tensile properties of tension-free vaginal tape and cadaveric fascia lata in an in vivo rat model. *BJU International*. 2004;**93**(1):171-173
- [53] Yildirim A, Basok EK, Gulpinar T, Gurbuz C, Zemheri E, Tokuc R. Tissue reactions of 5 sling materials and tissue material detachment strength of 4 synthetic mesh materials in a rabbit model. *The Journal of Urology*. 2005;**174**(5):2037-2040

- [54] Sultan AH. Anal incontinence after childbirth. *Current Opinion in Obstetrics and Gynecology*. 1997 Oct 1;**9**(5):320-4.
- [55] Rahn DD, White AB, Miller RT, Word RA, Wai CY. Effects of pregnancy, parturition, and anal sphincter transection on function of the external anal sphincter in an animal model. *Obstetrics & Gynecology*. 2009;**113**(4):909-916
- [56] Thakar R, Sultan AH. Management of obstetric anal sphincter injury. *The Obstetrician & Gynaecologist*. 2003;**5**(2):72-78
- [57] Rizvi RM. Assessment of experimental animal model for training obstetric anal sphincter injury techniques. *JPMA: The Journal of the Pakistan Medical Association*. 2013;**63**(1):103-105
- [58] Hajivassiliou CA, Carter KB, Finlay IG. Assessment of a novel implantable artificial anal sphincter. *Diseases of the Colon & Rectum*. 1997;**40**(6):711-717

