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Postpartum stress urinary incontinence: lessons from animal models

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Abstract

Postpartum stress urinary incontinence (SUI) is associated with chronic SUI in later life, which is 240% more likely to occur in women who deliver vaginally than those who did not. The etiology of SUI is multifactoral and has been associated with defects in both neuromuscular and structural components of continence. Specifically, clinical studies have demonstrated that pudendal nerve damage occurs during vaginal delivery, supporting the concept that neuromuscular damage to the continence mechanism can result in postpartum SUI. Urethral hypermobility and the loss of pelvic floor support, such as that involved in pelvic organ prolapse, have also been associated with SUI. Animal models provide an opportunity to investigate these injuries, individually and in combination, enabling researchers to gain further insight into their relative contributions to the development of SUI and the effectiveness of potential therapies for it. This article discusses the use of animal models of postpartum SUI in addition to the broad insights into treatment efficacy they provide.

Keywords

birth injury; continence; muscle injury; nerve injury; neuromuscular; regeneration; repair

Clinical relevance of animal models

Estimates of the prevalence of stress urinary incontinence (SUI) vary with differences in population samples and methods of statistical adjustment. Despite this variability, large epidemiological studies have established that SUI is approximately 240% more prevalent in women who underwent vaginal delivery compared with women who underwent cesarean section [1,2]. There also exists a strong association between antenatal SUI and postpartum SUI for primiparae [3-5]. Recent research has demonstrated that women who develop SUI during pregnancy are 579% more likely to have SUI 1 year postpartum [6]. Both antenatal and immediate postpartum SUI are predictive of chronic SUI. A total of 73% of women having SUI 3 months postpartum are incontinent 6 years postpartum [7-10]. Thus, a clear link exists between vaginal delivery and SUI, both immediately postpartum and later in life.

Conceptually, the urinary continence mechanism can be thought of as having two major components. The first is structural, the physical support of the urinary tract, and composed of

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the pelvic floor musculature and connective tissue; the second is neuromuscular, and consists of the pudendal nerve (PN) and external urethral sphincter (EUS) mechanism [11]. In vaginal deliveries, SUI is most likely to be the result of injury to both components. Damage to pelvic floor structures, specifically defects in the pubovisceral portion of the levator ani, are associated with SUI and can occur during vaginal delivery [12-14]. Likewise, antenatal and postpartum neurophysiological recordings demonstrate PN injury resulting from vaginal delivery but not cesarean section or pregnancy itself [7,15-18]. Thus, during vaginal delivery, injuries occur to both structural and neuromuscular components of the urinary continence mechanism. The clinical challenge is to determine the relative contributions of each component to the development of SUI and guide treatments accordingly.

Animal models of childbirth injuries facilitate not only the individual characterization of each of the childbirth injuries, but also specific combinations of structural or neuromuscular injuries. Furthermore, animal models enable investigation of the effects of related factors and comorbidities, such as diabetes, obesity, and steroid hormones, on the severity of childbirth injury and effectiveness of SUI therapies. This article details the insights gained from animal models of simulated childbirth into postpartum SUI.

Animal models of postpartum SUI & simulated childbirth injury

Rats

Rats have been most commonly utilized to study postpartum SUI [19-22]. The anatomy and physiology of the lower urinary tract and its neurological control have long been extensively studied in Sprague–Dawley rats [20-22]. Furthermore, following simulated childbirth injury, urodynamic changes mimic those seen clinically with vaginal delivery [23-25]. Specifically, rat models demonstrate rapidly decreasing urethral resistance to leakage, and significantly reduced leak point pressure (LPP), the bladder pressure at which leakage occurs in the absence of a bladder contraction [26-31].

While rodent models reproduce some physiologic aspects of SUI in humans, notable differences exist, the most relevant of which being that rats are quadrupeds while humans are bipeds. This results in a substantial difference in orientation of the bladder with regard to the pelvic floor. In humans, the bladder is cradled by the levator ani muscle complex, while in rats the bladder rests upon the peritoneal surface of the anterior abdominal wall [32]. Nonetheless, rodents can orient vertically by standing on their hind legs or can be placed in this position for study, possibly more closely reproducing human physiology. Thus, while additional contributions to continence may be afforded by the pelvic floor in humans, this may or may not be the case in rodents, potentially dependent upon the orientation of their body. Therefore, the primary component of continence in rats is probably the EUS, which makes it the key physiological mechanism tested in rodent models of postpartum SUI.

Injury models—Similar to humans, the PN innervates and controls the EUS in rats [20,21]. During childbirth, PN injury occurs in women and the resultant dysfunction, as evidenced by electrophysiological data, is associated clinically with SUI [7,15-18]. Thus, PN crush has been implemented as a recoverable neurogenic model of childbirth injury and postpartum incontinence in rats [25,33]. Since both the left and right PN innervate the EUS, bilateral injuries consistently reduce urethral resistance and simulate recoverable postpartum SUI while unilateral injury does not [23,34,35]. Ligation of the PN has also been studied as a model of SUI [36]. The use of periurethral botulinum-A toxin has been utilized to impair PN function and also to produce a recoverable model of SUI [37]. Last, unilateral and bilateral PN transection has been utilized, demonstrating decreased urethral resistance in a nonrecoverable manner since a piece of the nerve is usually removed in this model [35]. Thus, PN injury is a well-established model of neurogenic SUI in rats.

Along with damage to the neurological control of the EUS, direct sphincter injury has also been utilized to create rodent models of childbirth trauma and postpartum SUI. Since the urethra courses along the anterior vaginal wall and posteriorly to the pubic symphysis in humans, it is probably vulnerable to trauma during the second stage of labor [38]. This is supported by clinical data demonstrating that direct urethral injury occurs at higher rates in women delivering vaginally rather than by cesarean section [39]. Injury models such as urethrolysis, pubourethral ligament transection and electrocauterization of the EUS have been employed in rats to reproduce such trauma [31,40,41]. In the urethrolysis model, the length of the urethra is freed from the surrounding tissues, including the endopelvic fascia and anterior vaginal wall, beginning at its proximal end [31]. Similarly, transection of the pubourethral ligament results in a similar detachment and hypermobility of the urethra [40]. In the electrocauterization model, tissue lateral to the midurethra is cauterized, producing both muscle and nerve damage at that location [41]. Pharmacologic inhibition of urethral smooth muscle function has also been implemented using angiotensin I and II receptor inhibitors [42]. Aside from pharmacologic methods, these injury models each produce durable SUI, which does not recover acutely, similar to that observed with PN transection.

Simulated labor, or vaginal distension (VD), is also commonly used in rats to model postpartum SUI [22,24,27,43]. This method produces similar findings of reduced urethral resistance as in the targeted injury models previously discussed. VD is accomplished by inserting a modified-tip Foley catheter into the vagina with diameter and balloon volume adjusted according to rat size. Expansion of the balloon in the vagina simulates the second stage of labor, and damages the EUS, PN and tissues of the pelvic floor [44-46]. In addition, the model has been modified to include tension on the catheter in an attempt to simulate tissue stretching that occurs during delivery [27,43]. As with PN crush, postpartum incontinence in the VD model is recoverable [24,44]. Models consisting of VD combined with PN crush have recently been studied, providing valuable insight into the effects of simultaneous muscle and nerve injury, their synergistic effect on reducing LPP and the prolongation thereof, as well as their opposing effects on neuromuscular reneration [45-47].

Assessment methods—Stress urinary incontinence is defined as the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing and, thus, requires patient identification of leakage as involuntary [48]. Animal models therefore cannot recreate SUI according to its clinical definition. However, they can facilitate its study by reproducing mechanistic aspects of the condition since urethral resistance can be assessed in animal models using methods similar to clinical urodynamics. LPP, the measurement of bladder pressure during urine leakage, provides an assessment of urethral resistance. Significantly decreased LPP in the absence of a bladder contraction is associated with reduced urethral resistance and is presumed to simulate SUI in animal models, just as low bladder pressure during leakage in the absence of a detrusor contraction is clinically associated with SUI [49].

A variety of methods exist for assessing LPP in animals [50]. While somewhat dissimilar, each method in itself provides insight into the relative function of the continence mechanism. Direct bladder compression provides a straightforward means of testing urethral resistance independent of bladder contraction or overflow incontinence. Methods utilizing this technique vary from a closed abdominal approach to an open abdominal approach with direct bladder visualization [26,28,46]. Bladder pressure during compression can be recorded using either suprapubic or urethral catheters, with the latter contributing to urethral resistance [40,42]. While a straightforward method, factors such as angle of compression, speed of compression and bladder size may impact measurements. Nonetheless, a quantitative investigation of the variance in these measurements demonstrated consistency by those experienced with the technique [51].

Other methods used to increase bladder pressure include using a suprapubic catheter attached to a saline reservoir that is raised in height; however, this method probably measures overflow incontinence since the bladder fills rapidly with saline as the reservoir is raised and pressure increases [37]. In addition, in conjunction with the saline reservoir, tilt tables have been used to vertically orient the bladder and pelvis in a fashion similar to that of humans in order to incorporate gravity and evaluate both the urethral sphincter and pelvic floor continence mechanisms [29,30,52]. However, in these models spinal cord transection was performed to modulate reflexes, potentially reducing their utility for studying postpartum SUI.

Leak point pressure is a continuous measure of the severity of modeled incontinence. Similar to clinical urodynamics, abdominal pressure in the rat can be measured with a rectal catheter and can be used to assess levels of continence via measurement of abdominal LPP (ALPP) [31]. However, unlike that of humans, the rat abdomen is highly compliant and distensible, which may complicate the use of this measurement. The sneeze test is an alternative measure of urethral resistance that provides a dichotomous measure of continence, determining its presence or absence [22,27]. Investigation of the sneeze reflex in rats has demonstrated that rapid abdominal muscle contraction, as in humans, can produce urine leakage [53]. A comparison of methods showed that the sneeze test, in contrast to manual bladder compression or the tilt table method, induced an additional reflexive urethral closure mechanism, highlighting the involvement of supraspinal reflex pathways outside the bladder-to-EUS continence reflex [50]. Specifically, the EUS can be activated through the PN motor branch in two ways: as a result of supraspinal sneeze and cough reflexes or by the guarding reflex, a spinal circuit triggered by bladder afferents.

Measurements of urethral resistance and urethral closure have also been utilized to investigate function of the continence mechanism in rats. Urethral pressure profiles have been recorded using catheter withdrawal techniques [43]. Retrograde urethral perfusion pressure, the pressure required to open the urethra and fill the bladder via infusion into the distal urethra, assesses the strength with which tissues and the EUS coapt the urethra [31,42]. However, there is currently no evidence suggesting that retrograde opening pressure is the same as anterograde opening pressure, which likely possesses greater clinical utility. Anterograde opening pressure could be assessed via perfusion into the urethra through a transvesical catheter placed at the bladder neck [54].

Electrophysiological recordings of PN and EUS activity provide insight into their respective functionality, which teleologically are associated with urinary continence. Careful dissection of the PN motor branch permits its recording [46]. Likewise, the EUS can be recorded either with the blind insertion of electrodes and a closed abdomen or following full exposure by midline abdominal incision and transection of the pubic symphysis [23,35,46]. With concurrent LPP measurement, the changes observed in electrophysiological recordings have been quantified and the levels of neuromuscular function are associated with SUI and continence [35,46]. Such methods have provided useful insight into the neuromuscular mechanisms of urinary control.

Histological studies in rats also provide insight into the mech anisms of continence. Levels of fibrosis in the periurethral area have been assessed by imaging and are correlated with higher LPP and increased continence [55]. Likewise, following simulated childbirth injury, structural disruption of the EUS and PN have been associated with reduced LPP and presumed SUI [44,45]. Histological findings have also been linked with electrophysiological changes in EUS and PN activity [46,47]. Thus, an array of analysis methods exist for gaining detailed insights into the functional, structural and neuromuscular aspects of continence in the rat model.

Mice

Mice are increasingly being used as an animal model of postpartum SUI. Similar to rats, mice provide a small and cost-effective platform for research, but can challenge the translation of results to clinical practice since, like rats, they are quadrupeds and largely derive bladder support from the anterior abdominal wall and not the levator ani, as in humans [32]. Simulated childbirth injuries have been implemented in mice as have assessments of continence via bladder compression with intravesical pressure measured using a suprapubic catheter [56-59]. Compared to rats, mice require less space and resources to maintain, and offer an accelerated injury recovery time. However, their small size can increase the technical skill required for utilization in certain studies.

A strain of mice with lysyl oxidase like-1 (LOXL1) deficiency have been found to spontaneously develop pelvic organ prolapse (POP) following vaginal delivery, producing the first rodent model of POP [60,61]. Mice with fibulin-5 deficiency, as well as a colony of *UPII-SV40T* transgenic mice developed for studying bladder cancer, also spontaneously develop POP, even in nulliparous mice, that increases in severity following childbirth [62,63]. After POP, these mice experience lower peak voiding pressures and significant reductions in LPP with parity, probably a result of the loss of pelvic floor elasticity, another mechanism thought to contribute to SUI [58,59]. There is a characteristic perineal bulge resulting from the shifting of pelvic organs and occasional vaginal eversion [60]. Despite this difference from humans in location of the prolapse, the changes in connective tissue characteristics have been demonstrated to be relevant to clinical SUI [64]. Therefore, genetically modified mice are proving to be more useful for studying the full spectrum of pelvic floor disorders than are isolated injury models in rats or mice, which have not been shown to induce POP.

Domesticated animals

Domesticated animals present similar anatomical challenges as rodents – the lack of bipedal stature and the resultant differences in anatomical arrangement and structural physiology of the pelvic floor and lower urinary tract. However, unlike rodents, domesticated animals are larger, making the contributions from specific pelvic floor components easier to study. In addition, the structure of the pelvic floor is considered in some species to be more similar to humans than those of rodents [65,66]. However, the drawback to using larger models is greater cost and longer injury recovery time.

Rabbits have been utilized to study the contributions of the pelvic floor musculature to continence and voiding function since the domesticated rabbit has well-developed striated pelvic floor musculature, which is thought to resemble that of humans [65,66]. The urethral closure mechanisms involved with sneezing have also been investigated in felines, demonstrating urethral pressure increases at the locations of the EUS and levator ani with concurrent increases in electromyogram (EMG) activity in both muscles [67]. Similarly, ALPP has been utilized to study continence in canines [68]. More recently, a canine model of SUI due to sphincteric deficiency was created by the surgical removal of the EUS. Fluoroscopy and urethral pressure profilometry have been utilized in dogs, demonstrating the ability to utilize clinical diagnostics in larger animal models [69]. However, little work has been done simulating or studying childbirth injury in domesticated animal models, making the application and translation of these results to postpartum incontinence difficult.

Nonhuman primates

Nonhuman primates provide the closest approximation to human anatomy and physiology of any animal species [70]. While still mainly quadrupeds, the structure of the primate pelvis supports bipedal locomotion and upright posture. In addition, the primate pelvic floor may promote continence and support the urogenital system in a similar fashion to humans [71].

Being generally larger animals, a more precise study of individual pelvic floor components may be possible in primates. However, these studies require more space and resources than smaller animals. In addition, given their higher intelligence and communicable emotions, primate studies are subject to the highest ethical scrutiny of any animal in research.

Squirrel monkeys have been utilized to investigate POP following childbirth [72,73]. Surgical denervation of the levator ani muscle has also been used to model pelvic floor denervation and atrophy in these animals [74,75]. However, urologic function and SUI have not been studied in these animals or other primates.

Insights gained from animal models

Postpartum SUI can be investigated with a variety of animal models with diverse pathologies. As is clear from the previously described overview of the models, nerve injury, simulated delivery and the loss of physical support to the lower urinary tract all successfully recreate the pathophysiology of postpartum SUI. This mimics the findings in women, in whom PN damage, sphincteric insufficiency and urethral hypermobility have been implicated in the etiology of postpartum SUI [11]. As such, studying postpartum SUI in animal models has provided valuable insight into the etiologies and mechanisms of SUI and can be utilized for the development of potential therapies.

Basic animal models

PN injury

Varying degrees of PN injury have been studied using animal models. Crush injury induces a recoverable model of postpartum SUI, with LPP decreasing to a minimum value 4 days later and recovering to near-normal levels 2 weeks after injury [33,76]. Molecular evidence of PN regeneration supports this, as evidenced by β_{II}-tubulin expression, a neuronal cytoskeletal protein indicative of regeneration, which is significantly upregulated in the pudendal motoneuron cell body 1 week after injury but returns to normal by 2 weeks [34]. Ligation of the PN may create a pathophysiology similar to overactive bladder and postpartum SUI, since LPP was significantly reduced 4 weeks following ligation [36]. PN transection produces a durable model of SUI, with significantly reduced LPP persisting for 6 weeks after either unilateral or bilateral injury [35,46]. Furthermore, when comparing unilateral and bilateral PN transection, discrete contributions of each PN to LPP become clear, demonstrating the role of bilateral PN innervation in continence [35]. Therefore, it is apparent that the degree of PN injury directly determines both the severity of functional impairment as well as the duration of functional recovery.

As sufficient surgical isolation of the PN for either direct electrophysiological assessment of function or physical analysis of injury is clinically unfeasible, the application of these findings from animal studies to humans can be challenging. Clinical electro physiological studies involving the PN, reflex loops and muscle motor units currently provide the best means of translating this work, since associations between abnormal electrophysiological findings and SUI suggest that PN damage may be a factor in SUI development but are insufficient to demonstrate causation, and are limited by the aforementioned difficulties in isolating the nerve for study [17,18,77-81]. Nonetheless, a study in which action potentials were temporarily blocked suggests that the PN can contribute to the clinical manifestation of SUI [82].

The findings of direct electrophysiological studies of PN activity following injury in rats support the functional results from studies measuring LPP. A total of 4 days after PN crush, EMG amplitude and frequency, measures of overall muscle activity, are lowest [46]. A total of 3 weeks following PN crush, EMG activity remains significantly reduced compared with

normal; however, not to the degree observed acutely. This finding echoes the trend in LPP, which shows recovery 2 weeks after PN crush [33,76]. Electroneurography (ENG), direct recordings of PN electrical activity, demonstrates results similar to EMG with significantly reduced ENG activity 4 days after PN crush that recovers completely by 3 weeks [46]. Unilateral PN transection acutely produces a significant reduction in EMG activity, corresponding with a reduction in mean EMG amplitude and frequency, which is further reduced following transection of the remaining PN branch, leaving only low-amplitude spontaneous activity remaining [35,46]. However, 6 weeks after PN transection, EMG activity was partially recovered, but still significantly reduced compared with normal, suggesting nonpudendal collateral innervation of the EUS may be present [35,46]. These findings, which link changes in PN and EUS activity to varying severities of PN injury, provide valuable support to previous clinical studies associating abnormal electrophysiological findings with SUI and suggesting childbirth-related PN damage as an etiologic factor [17,18,77-81].

Vaginal distension

Vaginal distension simulates the second phase of labor, as the fetus passes through the birth canal and has been shown to damage both the EUS and distal PN branches [22,25]. Similar to PN crush, VD is a recoverable simulated childbirth injury, with increased duration from 1 to 4 h, prolonging the time to functional recovery [24,44]. EUS histology demonstrated damage compared with sham VD that was similar in severity across differing VD durations. Likewise, a study in mice analyzing the effect of VD balloon size demonstrated that larger balloons produced significantly greater reductions in LPP as well as significant decreases in the density of neurofilament immunoreactive nerves in the urethral sphincter [56]. Thus, VD has been verified to both functionally recreate SUI and produce diffuse pelvic floor injury, particularly to the EUS. The model has also been combined with subsequent ovariectomy to investigate postmenopausal incontinence, demonstrating that estrogen may reduce EUS degeneration following birth injury [23,43]. The translation of results from the VD model to clinical practice vary. Recent studies have shown that a prolonged second stage of labor is associated with postpartum incontinence, but increasing baby weight or macrosomia are not [39,83,84]. Regardless of the factors predisposing a patient to sphincteric injury and incontinence, this model provides a platform for research on regenerative therapies aimed at restoring EUS function after injury.

A study of blood flow to the urogenital organs also supports the presence of EUS injury in VD. During VD, blood flow to the bladder, urethra and vagina are significantly reduced, but rapidly restored after balloon deflation, yet smooth and striated muscle in the EUS as well as vaginal and bladder epithelium become hypoxic [85]. Hypoxia-inducible factor-α is upregulated in the urethra with increasing VD duration [86]. Together, these studies point to the susceptibility of the urethra, including the EUS, to hypoxic and/or reperfusion injury during delivery. Thus, these findings may provide mechanistic insight into the increased risk of postpartum incontinence associated with a prolonged second stage of labor [83]. Furthermore, with hypoxia identified as a causative factor for the expression of stem cell-homing factors, the potential for utilizing stem cells to replenish a diminished EUS or supply it with regenerative factors is promising [87].

Functional studies provide further evidence of VD-induced EUS trauma and differentiate it from potential concurrent PN injury. A total of 4 days following VD the active EUS response induced in sneezing, as well as EMG amplitude and frequency, are significantly reduced [46, 53]. By contrast, ENG recorded from the proximal PN showed no significant difference in frequency or amplitude following VD [46]. Furthermore, after VD, LPP decreases significantly and can take up to 3 weeks to recover, while PN crush produces changes in LPP that generally recover 2 weeks after injury [45,46]. Thus, VD produces a model of SUI different from and

independent of that induced by PN injury. As such, this raises the possibility of birth-induced sphincteric injury occurring independently of trauma-induced PN dysfunction, which may have clinical implications in situations where the absence of PN dysfunction and loss of pelvic support suggest sphincteric insufficiency [88].

Combined VD & PN injury

To create a more clinically relevant model of childbirth injury, VD and PN injury have recently been implemented in the same animal to create a combined model of childbirth injury [45-47]. Compared with either injury alone, the combined model provides valuable insight into the synergistic effects of simultaneous PN and VD injuries, as well as into the opposing effects of neural and muscular injury on neuromuscular recovery. Functional results demonstrate mixed results with some studies showing a significantly reduced LPP persisting beyond 3 weeks and another showing recovery by this time point [45,46]. Electrophysiological analyses of EUS EMG and PN ENG activity suggest that neuroregeneration is impaired in the dual injury model in comparison to either single injury. Specifically, EUS EMG amplitude and frequency are significantly reduced after PN crush, VD and dual injury, with dual injury being notably lower than either single injury 3 weeks later. Results from PN ENG were similar, with dual injury showing significantly reduced PN ENG frequency and amplitude 3 weeks after trauma compared with either single injury, both of which had recovered by this time. Thus, it is clear that dual injury produces a greater impairment of PN, and subsequently EUS function, compared with either single injury alone.

Peripheral nerve regeneration has been well studied, particularly with regard to neurotrophins, factors that promote neuroregeneration. One such molecule, brain-derived neurotrophic factor (BDNF), is upregulated in target organs and Schwann cells following peripheral nerve injury to facilitate regeneration via retrograde signaling [89-93]. The prolonged time for recovery observed after dual injury in comparison to either single injury alone is thought to be mediated by the differential effects of PN crush and VD on expression of BDNF in the EUS. Specifically, BDNF expression in the EUS decreases following VD but increases after PN crush [45]. Simultaneous VD may therefore be detrimental to PN recovery since the upregulation of BDNF required for neuroregeneration is impaired by EUS trauma [89-93]. Research into the effectiveness of supplementing the PN with BDNF to facilitate neuroregeneration after EUS injury is ongoing. Since injury to both the PN and EUS probably occurs in vaginal delivery, the potential for a treatment to foster PN recovery may impact the clinical approach to SUI treatment, shifting focus to regenerative neuromuscular therapy and potentially preventative intervention.

Direct sphincter injury

In addition to the sphincteric injury from VD and neurogenic dysfunction induced by PN injury, direct sphincter injury has been utilized to produce sphincteric incompetence as a more durable model of postpartum SUI. One such model, utilizing cauterization of the EUS and tissues directly lateral to the midurethra, produced a model of SUI that demonstrated significantly lower LPP throughout the 6-week study period [41]. Urethrolysis, the surgical dissection of the uretha from surrounding tissues, simulated SUI in rats that lasted through a 24-week period as measured by ALPP and retrograde urethral perfusion pressure [31]. Furthermore, histological analyses showed urethral atrophy of smooth and striated muscle as well as decreased innervation of the EUS, suggesting the SUI resulted in part from decreased innervation, atrophy and apoptosis of the EUS as well as a reduction in urethral support. A similar impairment of EUS function, although transient, was produced by periurethral injection of botulinum-A toxin [37]. These models have notable clinical utility with regard to direct sphincter injury occurring during vaginal delivery since urethral or bladder injury has been observed in approximately 3% of vaginal deliveries [39].

Similar to these models, sphincteric deficiency was produced in canines by the surgical removal of EUS tissue, which subsequently reduced LPP and bladder capacity throughout a 7-month study period [69]. Furthermore, the urethral pressure profile decreased at the location of the sphincter both with and without PN stimulation. Therefore, the surgical removal of EUS tissue successfully implemented sphincteric insufficiency in a canine model. Since EUS innervation remained intact in these studies, this model may prove beneficial for the development of regenerative therapies such as stem cells, growth factors and other means of restoring EUS muscle bulk that is reduced in women with SUI and lost as a result of childbirth injury and aging [94,95].

Urethral hypermobility

The effects of urethral hypermobility on continence have been studied using a rat model of pubourethral ligament transection. This model demonstrates consistently reduced LPP from 4 days to 4 weeks following transection, with a magnitude of reduction similar to that noted after PN transection [40,96]. Thus, pubourethral ligament transection creates a durable model of SUI owing to a reduction in urethral support. Further studies are required to assess the neuromuscular intactness of the PN–EUS mechanism following this intervention as well as the effects of treatments aimed at restoring LPP. With controversy regarding the use of currently available sling and tape procedures in women of reproductive age, this model may prove useful for developing more durable solutions to postpartum incontinence for use in women of reproductive age [97-99].

Connective tissue homeostasis has been investigated with regard to pelvic floor and urethral support, each of which contributes significantly to continence. A recent study demonstrated that the urethra loses stiffness and elasticity following VD [100]. Specifically, in pregnant and nonpregnant mice, VD induced visible elastic fiber disruption and fragmentation. Furthermore, matrix metalloproteinases (MMPs), specifically MMP-2 and MMP-9, enzymes responsible for elastic fiber degradation, increased in activity following VD. However, tropoelastin and fibulin-5, proteins responsible for elastic fiber assembly, were only upregulated in pregnant mice [101,102]. Since fibulin-5-deficient mice experience spontaneous POP following distension, these results suggest that pregnancy may produce a protective effect, inducing elastic fiber restoration following distension associated with delivery. With steroid hormone levels varying substantially during pregnancy, estrogen may play a part in this protective effect, as clinical studies have demonstrated the importance of its role in connective tissue homeostasis [103]. Therefore, the animal models may provide beneficial insights and foster development of therapies aimed at the future prevention or treatment of postpartum SUI.

Genetic studies have shown that genes influencing connective tissue homeostasis may also play a role in the development of postpartum SUI. Expression studies in urethral tissues 12 weeks following VD, with ovariectomy the following week, demonstrate significant upregulation of multiple gene superfamilies [104]. Of particular interest were MMP13 (an enzyme responsible for collagen breakdown), RGS2 (a negative regulator of smooth muscle cell contraction) and SMAD2 (a mediator of inflammation), all of which were significantly overexpressed in animals that developed SUI compared with those that did not [104]. Relative to expression in continent rats, the overexpression of these molecules suggests that collagen breakdown, smooth muscle relaxation and inflammation are induced by VD, all of which would facilitate the development of SUI owing to a loss of urinary tract support. Clinical correlates of this study have been performed in women by many investigators and have demonstrated differential expression of genes regulating connective tissue in women with SUI and/or POP compared with those without [103,105,106]. An ongoing study using linkage analysis investigated the possible existence of genes predisposing women to SUI [107]. Therefore, animal models will probably prove valuable in upcoming years for the development and testing

of treatments to restore connective tissue homeostasis with the goal of treating or preventing postpartum and chronic SUI.

Models of comorbiditiy

Pelvic organ prolapse

The role of pelvic floor support in maintaining continence and the molecular mechanisms of POP development have been investigated using mice that spontaneously develop POP following natural birth. Even without vertical body orientation, mice deficient in LOXL-1, an enzyme required for synthesizing elastin polymers, develop POP after delivery and have significantly reduced LPP that worsens with parity when compared with nonprolapsed, wild-type mice [58,59]. Upon histological analysis, the EUS in prolapsed mice contains significantly more elastin clusters, signifying dysfunctional elastin production, compared with wild-type controls. In addition, POP has been studied in mice with fibulin-5 deficiency and a colony of *UPII-SV40T* transgenic mice that spontaneously develop POP even before delivering pups [62,63]. Prolapse in these rodents consists of a large perineal bulge and only occasionally vaginal eversion [60], as is more commonly observed in women. Nonetheless, the changes occurring in connective tissue homeostasis have been demonstrated to be relevant to SUI in women [64]. Spontaneous POP has been studied in the squirrel monkey, as have the effects of levator ani denervation on pelvic support [73,75]. Urologic analyses of these animals have yet to be published, however. Nonetheless, the development of POP and its role in the development of SUI can be successfully studied in animal models, as demonstrated in mice.

Diabetes

To better understand factors predisposing women to postpartum SUI, a variety of conditions clinically associated with it have been studied using animal models. The effects of diabetes mellitus (DM) on postpartum SUI have been investigated using VD and a model of Type I DM induced by intraperitoneal streptozotocin injection. Compared with nondiabetic rats, those with DM had significantly lower LPP following VD and prolonged time to recovery [108]. EUS histology revealed more severe sphincteric disruption after VD in animals with DM compared with nondiabetic rats. Clinical studies of Type I DM and incontinence are largely epidemiological and have provided initial insights into aspects of DM associated with incontinence [109-112]. An established animal model of Type I DM will likely prove valuable in studying the specific pathophysiological changes occurring in structures providing continence, such as the EUS, PN and pelvic floor musculature.

Characterization of the effects of Type II DM and obesity on PN function is ongoing [113]. Obesity was found to significantly impair EUS function and recovery following PN crush injury. Specifically, EUS EMG activity was reduced at rest and during LPP compared with non-obese animals. Likewise, obesity with DM significantly reduced resting EMG activity and impaired recovery of EUS activity following PN crush. Patterns in PN ENG data were similar, with obesity impairing recovery of PN activity after crush, and obesity with DM significantly reducing PN activity in uninjured animals. These results suggest that obesity may impair sphincteric function and impair neuroregeneration while DM may induce PN dysfunction, possibly through a mechanism similar to diabetic peripheral neuropathy [113]. These findings support those of clinical studies that demonstrate associations between Type II DM and varying types of incontinence, which also show an association between gestational DM and SUI [112,114-117]. Furthermore, nerve dysfunction in animal models suggests that diabetic peripheral neuropathy may provide a mechanism for the association between the duration of Type II DM and SUI [115].

Postpartum SUI treatment & prevention

Neuromuscular treatments

Factors influencing the restoration of functional urethral resistance and neuroregeneration have been studied in animal models to identify potential therapies for treating and preventing SUI. Intravenous angiotensin II successfully restored retrograde LPP following either urethrolysis or PN transection [42]. It therefore has a potential therapeutic role in stimulating smooth muscle to treat SUI from severe injury of the neuromuscular continence system.

Estrogen has also been studied in regard to postpartum incontinence. LPP in rats treated with estrogen recovered significantly faster than animals deficient in estrogen [118]. These results were further supported by the demonstration of significantly greater expression of β_{II}-tubulin, a marker of neuroregeneration, in the PN motor neuron cell bodies of rats treated with estrogen compared with saline. Furthermore, histological studies have demonstrated a neuroprotective, and possibly neuroregenerative, effect of estrogen in PN recovery following crush injury [119]. Similarly, models of ovariectomy-induced menopause have also shown that estrogen potentially reduces the severity of sphincteric degeneration after VD [27,43]. As discussed previously, it has been well established clinically that estrogen plays a key role in the homeostasis of connective tissues of the urethra and pelvic floor [103]. Basic science literature has characterized the regenerative and protective effects of estrogen on both central and peripheral nerves [120], similar to that of testosterone [121]. Thus, it is possible that estrogen or other hormones may protect against postpartum SUI related to PN damage.

Peripheral nerve regeneration has been described in neuroscience literature with regard to the direct supplementation of neurotrophins to injury sites [89-93]. Recently, a study of the administration of exogenous BDNF to the PN after dual simulated childbirth injuries demonstrated that significantly reduced LPP persists for 2 weeks when the injury is treated with saline but not when treated with BDNF [122]. In addition, EMG amplitude and frequency were significantly reduced at rest with saline treatment but not with BDNF administration. Supplemental BDNF has shown little to no benefit for recovery from PN crush alone, which is likely due to injury-induced upregulation of endogenous BDNF by the EUS.

In addition to direct neurotrophin supplementation, electrical stimulation of the PN for 1 h following dual injury significantly increased BDNF expression in PN cell bodies 1 and 2 weeks following injury compared with sham stimulation [123]. Furthermore, 1 week after injury and stimulation, β_{II}-tubulin was significantly upregulated by stimulation compared with sham stimulation, suggesting improved neuroregeneration occurred with electrical stimulation. Clinically, nonselective transvaginal electrical stimulation of the pudendal nerve has been found to be as effective as other noninvasive therapies for treating SUI [124,125]. However, larger clinical trials of this method are needed to determine its efficacy and the target patient population. This approach may provide an avenue for preventing the development of postpartum SUI when used after delivery.

Surgical interventions

Pudendal nerve transection creates a long-term, postpartum SUI model useful for the study of corrective treatments. A vaginal sling procedure involving vaginal dissection and the deployment of a synthetic sling was performed in rats following PN transection [126]. The sling acutely restored LPP to normal values compared with significantly reduced LPP after PN transection and sham sling implantation [126]. Similar results were found 2 weeks after transection and sling implant ation in another study using intestinal submucosal slings with or without muscle-derived cell seeding [127]. The differences in LPP persisted for 5 weeks after transection, with the sling still providing recovered LPP compared with that in sham-treated

animals [128]. No differences in LPP were found between intact slings and slings cut completely at the midurethra during implantation. Further study demonstrated similar inflammatory, edematous and collagenous changes at the site of the intact and cut slings, likely explaining the benefit to continence provided by each [55,129]. These results echo those observed clinically in which sling surgery has proven a successful means of treating SUI in women [130-132]. The results of sling lysis differ, however, as the recurrence of SUI following sling incision occurs at a rate higher than that observed in the animal models [133-135]. The effects of prolapse reduction surgery on continence in animal models have yet to be investigated. As novel sling materials and designs are developed, an established animal model of sling implantation may prove useful for preclinical investigation of these therapies.

Cell-based therapies

Stem cells are an active area of research pertaining to the treatment and prevention of SUI. Periurethral injection of cell-based therapy has also been studied in nerve transection models. Following bilateral sciatic nerve transection proximal to the PN branch point, rats were given injections of either saline, muscle-derived progenitor cells (MDCs) and/or fibroblasts in various dosages [29,52,136]. Compared with uninjured animals, LPP was significantly reduced after PN transection when treated with saline injection but not when treated with MDCs and/or fibroblasts [29,52]. A positive dose–response relationship with cell concentration existed, and animals receiving the highest dose of fibroblasts developed bladder outlet obstruction. Functional analyses of urethral strips demonstrated significantly reduced EUS fast-twitch contraction strength with saline treatment, but significant improvement in contractility with fibroblast and MDC treatments [52,136]. Recent research has confirmed these results using human muscle-derived cells in athymic rats [137].

Multipotent cells from human lipoaspirate also remain viable and may facilitate recovery from SUI when injected into the lower urinary tract of rats and mice, providing a possible alternative to MDC treatments [138-140]. The primary mechanism of action of these cells is thought to be paracrine in nature [140]. Further work is needed to fully gauge the clinical potential of lipoaspirate-derived cells as this research is relatively new.

A similar study utilized cauterization of the EUS and tissues lateral to the midurethra to investigate the effectiveness of MDC injection [141]. Periurethral treatment with MDCs restored LPP 4 weeks later while animals receiving sham treatment had not recovered 6 weeks after injury. MDC treatment produced a continuous striated layer of EUS muscle consisting of both injected MDCs and endogenous cells. In addition, more nerves were present in the MDC-treated group than the sham-treated group. Collectively, the results of these studies suggest that muscle-derived and fat-derived cells may foster EUS functional recovery following PN injury while fibroblasts may simply provide a passive bulking effect similar to collagen or other injectable agents. Results from a preliminary clinical trial of cellular injection have shown promise, with no serious adverse events and both full and partial resolution of SUI after MDC treatment [142]. This developing field is an area demonstrating successful translation of work from animal models to clinical applications.

In addition to the direct utilization of cells, treatment with paracrine factors produced by stem cells or the systemic infusion of stem cells may provide an alternative means of treating or preventing postpartum SUI. Hydrogel microspheres impregnated with bFGF continuously deliver the molecular treatment over 2 weeks [37]. Compared with rats receiving hydrogel without bFGF, rats receiving bFGF after periurethral botulinum-A toxin injection demonstrated significantly increased LPP 4 weeks following injection [37]. Furthermore, bFGF produced significantly increased thickness of EUS smooth and striated muscle. Thus it appears that similar to the direct administration of stem cells to the EUS, bFGF can improve muscular recovery and possibly prevent the development of SUI due to transient denervation.

As such, this form of regenerative treatment may appeal in clinical situations in which the utilization of stem cells is not practical or feasible.

Gene expression with regard to stem cell-homing cytokines has been analyzed in urethral tissue following VD in rats. A 20-fold increase in urethral expression of mRNA of monocyte chemotactic factor 3, a stem cell-homing cytokine, was observed immediately after VD and decreased to a sixfold increase by 24 h after injury [143]. Similar results were found in a different rat strain, with a 25-fold increase in urethral expression following VD [144]. Investigation of the effect of VD duration demonstrated a significant positive relationship between urethral expression of monocyte chemotactic factor 3 mRNA, two of its receptors CCR-1 and CCR-5, and the duration of VD [86]. Therefore, it appears that VD results in the urethral expression of cytokines that attract stem cells to injured tissues to facilitate recovery following childbirth injury. However, these gene-expression results are based upon mRNA levels, and protein levels were not investigated [86,143,144]. Nonetheless, these data suggest that it may not be necessary to utilize periurethral injection following delivery, but rather utilize systemic administration of stem cells, taking advantage of the natural cytokine upregulation and homing of stem cells induced by childbirth injury.

Expert commentary

Animal models of SUI have focused on recreating the neuromuscular deficiency and the loss of pelvic floor support seen clinically. Whether implemented through surgical trauma, pharmacologic manipulation, simulated birth, or vaginal delivery, these techniques have enabled further study of the mechanisms by which each contributes to the multifactoral nature of SUI. They have also provided valuable insight into treatments and their efficacy, mechanisms and targets of action.

Pudendal nerve injury has been shown to occur clinically and has been well characterized in animal models. Damage to the neuromuscular continence mechanism incurred through nerve injury produces sphincteric deficiency as evidenced by reduced resistance to leakage and decreased activity of the PN and urethral sphincter. Furthermore, when combined with injury to the sphincter, the effects of PN injury take longer to recover than if the nerve alone was injured, probably due to insufficient upregulation of BDNF by the EUS. Ongoing research is therefore investigating methods of improving neuroregeneration by manipulating neurotrophins, and has produced initial results that appear promising.

In addition to inducing sphincteric dysfunction through impaired urethral sphincter innervation, direct sphincter injury using cauterization, urethrolysis, or functional inhibition with botulinum toxin or angiotensin receptor blockers, have also successfully replicated SUI. Such models have been utilized to study the efficacy of stem cells and growth factors as therapy for incontinence. Periurethral injection of muscle-derived or adipose-derived stem cells, as well as paracrine growth factors, have proven beneficial in increasing urethral resistance to leakage. Furthermore, as opposed to standard bulking agents such as collagen, which dissipate and lose efficacy with time, precursor cells or growth factors produce lasting improvements in continence by enhancing urethral sphincter musculature. Thus, the use of such injectable therapies may provide improved outcomes in the clinical setting by stimulating the growth of functional tissue rather than providing only passive bulking.

The loss of structural support of the lower urinary tract by pubourethral ligament transection replicates urethral hypermobility and causes an SUI-like state in rodents that can be corrected with sling procedures, as is the case in humans. Furthermore, studies of the effects of sling lysis have shown that continence persists following sling lysis, suggesting continence is maintained by the development of inflammatory and connective tissue that may increase tissue stiffness in the region of the sling surrounding the urethra. Similar to the loss of urethral support,

decreased pelvic floor integrity has also been shown to contribute to incontinence. Animal models of POP have demonstrated that an inverse relationship exists between LPP and parity. While POP can be surgically repaired in humans, such procedures have not been attempted in rodent models. However, research focusing on the ability of nonautologous stem cells to compensate for genetically induced POP is ongoing.

Overall, the use of animal models of postpartum SUI has provided great insight into the pathophysiology of SUI. Specifically, the ability to simulate and study individual and combined childbirth injuries has stimulated research aimed at identifying improved treatments for each. As work in this field continues, the multifactoral nature of SUI will probably lead to research on multicomponent therapies that target the many etiologic components of the condition and provide maximal therapeutic benefit.

Five-year view

Current research is largely focused on short-term, recoverable models of postpartum SUI. Clinically, postpartum SUI is strongly associated with the recurrence of SUI in both the short and long term. Understanding the link between the two conditions will be an important area of study in the upcoming years. However, recurrent SUI in animal models has not been demonstrated. Therefore, the creation of a model that replicates the link or progression from postpartum to chronic SUI is in need of development for animal studies to fully characterize the spectrum of SUI and provide maximal insight into its development and means of prevention and treatment.

With regard to current therapies and the understanding of the pathophysiology underlying SUI, knowledge of the contributions of various injuries to the development of postpartum SUI has been acquired. Current surgical treatments are successful at reestablishing pelvic floor support and minimally invasive injectable treatments can provide temporary improvement in urethral resistance. However, no current therapies restore sphincteric function or provide durable urethral bulking. Current research on targeted neuroregenerative therapies has shown exciting results with improvement in urethral sphincteric function. Furthermore, investigation of cell-based injectable therapy has been shown not only to provide durable bulking, but also to produce an increase in functional muscle in the urethral sphincter.

Over the next 5 years, significant progress in the development of therapies targeting the neuromuscular mechanisms of continence will continue. These treatments will probably be aimed at both preventing the development of SUI following childbirth injury as well as improving recovery from postpartum and chronic SUI. As such, supplements to the current surgical approaches to SUI will be a major focus of research in the upcoming years.

Finally, current work highlights the multifactoral etiology of SUI and raises the possibility that the diagnosis of SUI may evolve to become more specific, extending beyond the current diagnoses of prolapse, urethral hypermobility and sphincteric insufficiency. For example, in the future sphincteric insufficiency may be classified into either sphincteric denervation or muscular injury, encompassing both aspects of the neuromuscular continence mechanism, and recognizing that each contributes independently to continence and must be treated differently. The fields of basic and translational research in postpartum SUI are rapidly progressing and gaining insights into the condition. With the growing focus on regenerative therapies, the management of SUI may change radically.

Key issues

- Animal models facilitate the study of individual aspects of complicated clinical injuries such as childbirth, furthering our understanding of their intricacies.

- Mechanistic and invasive studies unable to be completed in humans can be performed using animal models, enabling elucidation of the causation of pathologies.
- Animal models enable preclinical investigation of potential therapies targeting specific injuries, facilitating the development of improved treatments for incontinence.
- Simulated birth trauma is necessary in animal models owing to their relatively atraumatic natural birth, thus only approximations of human birth can be made.
- Quadruped models have pelvic orientation dissimilar to humans, challenging the translation of results from animals to humans.
- Rodent models of simulated childbirth approximate the clinical findings in stress urinary incontinence (SUI), enabling the use urodynamic evaluations to assess injuries and treatments.
- Genetic models of pelvic floor dysfunction in animals suggest that connective tissue homeostasis contributes to the development of SUI, similar to that noted in humans.
- The effects of comorbidities on the pathogenesis of SUI can be investigated in a controlled and replicable fashion using animal models, in contrast to clinical research.
- Animals at least temporarily recover from SUI, unlike most humans with the chronic condition, which indicates the need for longer term animal studies to determine if recurrence occurs, similar to perimenopausal incontinence in women.
- The neurological control of continence in rodents is extensively studied, facilitating investigation of various etiologies of neurogenic SUI in these animals.

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