Published in final edited form as:

Curr Opin Obstet Gynecol. 2010 October ; 22(5): 425–429. doi:10.1097/GCO.0b013e32833e499d.

Neurogenic aspects of stress urinary incontinence

Kamran P. Sajadi^a, Bradley C. Gill^{b,c}, and Margot S. Damaser^{a,b,c}

^aGlickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio, USA

^bCleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, Ohio, USA

^cDepartment of Biomedical Engineering, Cleveland Clinic, Cleveland, Ohio, USA

Abstract

Purpose of review—Vaginal childbirth is a significant risk factor for stress urinary incontinence (SUI). Women with SUI demonstrate dysfunction of the pelvic floor and pudendal nerve. Animal models of SUI have been developed to investigate its pathophysiology and for preclinical testing of potential treatments.

Recent findings—Vaginal distension, a method of simulating childbirth injury in animals, produces a reliable decrease in leak point pressure (LPP), a measure of urethral resistance to leakage and quantification of SUI severity in animals. In addition to ischemia and direct tissue damage, vaginal distension causes denervation of the external urethral sphincter (EUS). Pudendal nerve crush produces a similar decrease in LPP, whereas combined PNC and vaginal distension injury delays recovery of LPP compared with either single injury alone. Neurophysiologic studies have elucidated the results of each injury and their combination on pudendal nerve and EUS function. Urethrolisis, electrocautery, and pudendal nerve transection produce more durable functional impairment via both structural damage and denervation. Pubourethral ligament injury eliminates the structural support of the urethra, but its neurologic effects are unknown.

Summary—Animal models demonstrate a complex interplay between tissue damage and pudendal nerve dysfunction, and provide insight into the importance of neuroregeneration in the recovery of continence.

Keywords

animal; childbirth injury; disease models; pudendal nerve; stress; urinary incontinence

Introduction

Stress urinary incontinence (SUI), defined as the ‘involuntary loss of urine on effort or physical exertion ... or on sneezing or coughing’, is a common disorder [1]. The prevalence of urinary incontinence varies by the population studied and definition used, with most studies reporting that 25–45% of women have incontinence, with approximately half reporting SUI [2]. There are multiple risk factors for SUI in women, including state of health, obesity, smoking, age, and surgical trauma, but among the most important are pregnancy and vaginal childbirth [3,4].

Clinical evidence suggests that vaginal childbirth injury results in neuromuscular and ischemic damage in the bladder outlet and urethra, which contribute to the subsequent risk

of developing SUI [5]. Damage to the ligaments, fascial support, and pelvic floor musculature, including the levator ani, also occurs with vaginal childbirth and is associated with SUI [6]. In addition, the pudendal nerve, which projects from Onuf's nucleus and traverses Alcock's canal before entering the ischiorectal fossa and innervating the external urethral sphincter (EUS), is susceptible to injury during vaginal childbirth, particularly as it passes between the sacrospinous and sacrotuberous ligaments [7]. In addition to nerve compression, a three-dimensional model of vaginal childbirth has demonstrated that significant stretch of the pudendal nerve may occur, with a 13% elongation occurring in the motor branch to the EUS [8]. Physiologically, experiments using rat tibial nerves have demonstrated decreased nerve perfusion at 8% stretch and complete ischemia at 15% stretch [9]. Thus, pudendal nerve ischemia likely occurs during vaginal delivery as a result of both stretch and compression.

Increased pudendal nerve terminal motor latency, an indicator of nerve damage or dysfunction, is correlated with vaginal delivery, advanced age, and SUI [7,10]. Women with SUI diagnosed by urodynamics also demonstrate pudendal nerve dysfunction as evidenced by abnormal nerve conduction velocity and EUS electro-myography (EMG) [11]. Five years after vaginal delivery, persistently prolonged pudendal nerve terminal motor latency was more marked in women with SUI [7,12]. Additionally, the external anal sphincters in these women showed abnormal fiber densities, suggesting partial reinnervation occurred following pudendal nerve injury [12].

Clinical and epidemiological data are useful for hypothesizing the pathophysiology of SUI, but human studies do not allow the direct study of cause-and-effect mechanistic relationships under controlled circumstances. Therefore, a variety of animal models of SUI have been developed. These models are important to improve our understanding of the mechanisms of SUI development and to provide a means of preclinical testing of new treatments. There are some limitations to animal models, however. For example, SUI is defined as unintentional urine loss, but animals cannot communicate intent [1]. In addition, measures of urethral resistance to leakage in animals require anesthesia, which may itself affect the neuromuscular mechanisms of continence [13]. Finally, the animals used in all models are quadrupeds, whereas humans are bipeds. This is particularly relevant as the human bladder rests against the levator ani complex, which provides ancillary continence via urethral support, whereas in quadrupeds the bladder rests upon the anterior abdominal wall [14]. Therefore, the primary continence mechanism in quadrupeds is likely the EUS, which as a result is the primary organ of interest in most animal models of SUI. Despite these limitations, animal models are reproducible and allow invasive and mechanistic investigations of the lower urinary tract and pelvic floor that are not possible in humans.

Surrogate measures of stress urinary incontinence

Because animals cannot complain of undesired leakage *per se*, several laboratory tests to detect and/or quantitate decreased urethral resistance have been developed.

Sneeze test

SUI was initially identified by triggering a sneeze reflex in rats and assessing for urinary leakage [15]. An irritant, such as chilli powder or a clipped whisker, was placed in the rodent's nose, inducing a sneeze, and leakage was subsequently noted in 30% of animals that underwent simulated childbirth injury but none of the uninjured controls. This technique has also been utilized in feline models [16].

Leak point pressure testing

Manual leak point pressure (LPP) assessment involves the placement of a bladder catheter and, under anesthesia, the application of a Crede maneuver to the abdomen while measuring the bladder pressure at which leakage occurs [17]. This method has gained popularity because it is relatively easy to implement, reproducible, and quantifiable [17,18,19*,20*,21]. Importantly, as opposed to testing for the presence or absence of leakage, control animals have a measurable LPP, facilitating statistical comparisons among injuries and/or treatment groups.

Vertical tilt table leak point pressure testing

In an effort to replicate the erect position of humans, a rodent may be secured to a vertical tilt table to assess LPP [22]. The results of this technique are similar, repeatable, and comparable to those from manual LPP assessment [23]. Using this method, the spinal cord is often transected to eliminate suprasacral voiding reflexes. This, in turn, abolishes any central regulation of Onuf's nucleus and other spinal reflex centers important for continence [24]. In short, the advantage of a more human-like, erect posture must be weighed against the potential confounding factors of spinal cord transection.

Electrical stimulation leak point pressure testing

Electrical stimulation of abdominal muscles has been used to induce a sudden increase in abdominal pressure, as opposed to the gradual increase elicited by manual LPP testing. Using this method, Kamo and Hashimoto [25] demonstrated that reflex urethral closure mechanisms via bladder–spinal cord–urethral sphincter reflexes and pelvic floor muscles produce a reflexive increase in urethral resistance that maintains continence. However, like tilt table testing, electrical stimulation LPP testing is limited by the need for spinal cord transection to prevent supraspinal regulation of continence. Furthermore, despite application of maximum stimulation, some animals do not demonstrate urinary leakage, making quantitative comparisons between groups difficult with this method [25].

Urethral closure pressure testing

Urethral pressure profilometry in animal models has been performed using catheter withdrawal techniques, similar to those utilized clinically [26]. Retrograde urethral perfusion pressure (RUPP) testing uses a catheter inserted only through the urethral meatus and secured with a watertight suture to measure variations in intraurethral pressure with flow as a surrogate for urethral resistance [27]. Advantages of RUPP are that it is not operator-dependent and does not require a suprapubic catheter [27]. Retrograde flow, however, is nonphysiologic. Urethral closure pressure can be assessed with antegrade flow via a suprapubic catheter advanced to and wedged within the bladder neck [28].

Animal models of stress urinary incontinence

In women, the mechanisms of SUI development from vaginal childbirth injury are believed to be neurologic, ischemic, and via direct tissue damage. Animal models have been designed to replicate each of these mechanisms.

Vaginal distension

One of the most common models of SUI is vaginal distension in the rat, which was first described in 1998 [15]. To replicate the distension of the vagina that occurs during the second stage of labor, the rat vagina is gently dilated before a modified balloon catheter is placed within it and inflated [15]. In human labor, pressure against the pelvic sidewall can reach up to 240 cmH₂O [29], and vaginal distension aims to replicate this phenomenon. The

duration of the procedure is important [17,30], as a prolonged second stage of labor, particularly greater than 1 h, has been shown to be a significant risk factor for SUI in women [10]. Vaginal distension generates reproducible decreases in LPP, which nadir 4 days after injury [30]. This minimum is similar whether the duration of vaginal distension is 1 or 4 h; however, longer distension duration slows the recovery of LPP [30]. Vaginal distension produces thinning and disruption of the smooth muscle between the vagina and urethra and causes edema in the levator muscles [15]. It also decreases blood flow to the urethra and vagina and increases urethral expression of hypoxia-inducible factor 1 α (HIF1 α) [18,31]. In addition, vaginal distension increases the expression of stem cell homing cytokines, specifically monocyte chemoattractant protein-3 (MCP-3) and receptors, in both inbred and outbred rat strains [32[•]].

Vaginal distension also contributes directly to neurogenic injury, as demonstrated by increased c-Fos expression, a nonspecific marker of neuronal injury, in the dorsal horns of spinal segments L6 and S1 following vaginal distension in rats [15]. Likewise, the density of urethral sphincter neurofilaments was decreased after vaginal distension in a mouse model, but returned to normal, suggesting a partial denervation injury [19[•]]. Brain-derived neurotrophic factor (BDNF), a neurotrophin necessary for neuroregeneration [33], is downregulated in the EUS 1 day after vaginal distension with a concurrent increase in the presence of degenerated nerve fascicles [34[•]].

Pudendal nerve injury

In the rat, pudendal nerve dysfunction resulting from childbirth injury has been simulated using pudendal nerve crush (PNC). PNC is performed in both the left and right ischiorectal fossae proximal to the innervation of the EUS due to the bilateral innervation of the musculature. PNC produces a predictable decrease in LPP that nadirs at 4 days and recovers by 2 weeks [35]. One day after injury, the EUS shows an increased expression of numerous neurotrophins, including BDNF, neurotrophin-4 (NT-4), and nerve growth factor [34[•]]. Histologic studies 2 weeks after injury demonstrate degenerating and regenerating nerve fascicles, suggesting that, although functional recovery (according to LPP) has been achieved, neurologic recovery continues, which has been observed as long as 6 weeks after injury [35]. PNC also produces a significant decrease in electrophysiologic activity of the neuromuscular continence mechanism as evidenced by decreased muscle and nerve activity in EUS EMG and pudendal nerve motor branch potentials (PNMBPs) [36[•]]. In contrast, vaginal distension resulted in decreased EUS EMG activity, but not PNMBP, suggesting that the neurogenic dysfunction from vaginal distension is due to distal nerve fascicle, neuromuscular junction, or sphincteric injury. In fact, fluorescent labeling with α -bungarotoxin following vaginal distension shows denervated motor endplates with a concomitant loss of neuromuscular junction organization, and the persistence of normal endplates, indicating an incomplete neurologic injury [37]. Following PNC, there is a similar pattern of mild motor endplate diffusion coupled with thin, tortuous renerivating axons [37].

The dual injury model

To better replicate the neurologic and mechanical trauma involved in vaginal childbirth injury, a dual injury model consisting of vaginal distension and PNC was developed to study the differential and combinatorial effects of each injury [36[•]]. Recovery of LPP following the combined injury occurred by 6 weeks, compared with 3 weeks following either injury alone [36[•]]. PNMBP were normal after vaginal distension, whereas EUS EMG was dysfunctional, indicating that nerve injury incurred during vaginal distension likely occurs in the most peripheral part of the pudendal nerve [36[•]]. Another study without electrophysiological testing, requiring significantly less surgical dissection, demonstrated that recovery of LPP in the dual injury group occurred 3 weeks after injury, compared with

10 days for vaginal distension alone [34^{••}]. In this study, BDNF and NT-4 expression was found to be upregulated after dual injury, but notably less than from PNC alone [34^{••}]. Despite functional recovery, striations in the EUS musculature were less clear and trim than in uninjured controls, and small myelinated axons distal to the site of PNC demonstrated distorted myelin figures and Wallerian degeneration, suggesting that neuroregeneration was still incomplete at 6 weeks despite restoration of LPP [34^{••},38^{••}].

Pudendal nerve transection

Pudendal nerve transection (PNT) is the most severe form of pudendal nerve injury. Following bilateral PNT, LPP decreases significantly 4 days after injury and does not recover even 6 weeks later [36^{••}]. Furthermore, EUS EMG activity and PNMBP activity remain practically eliminated 6 weeks after bilateral PNT, with EUS histology showing atrophy of the EUS [38^{••}]. This lack of recovery after PNT confirms the absence of extrapudendal innervation to the continence mechanism [36^{••}].

Models simulating anatomic support damage

Rather than directly attempting to replicate vaginal delivery, the normal anatomic support structures of the urethra have been disrupted to simulate childbirth injury and create durable models of SUI in animals.

Urethrolisis

Urethrolisis is performed transvaginally or retropubically in humans for voiding dysfunction after anti-incontinence procedures [39]. In rats, freeing the proximal urethra from its fascial attachments through a transabdominal approach has been used to produce SUI, as measured by LPP and RUPP, which persists for up to 24 weeks [27]. In addition to the induced structural changes, decreased urethral smooth muscle content, increased apoptosis, and a time-dependent loss of neuronal content was observed, suggesting a component of denervation injury present in the model [27].

Pubourethral ligament injury

In an effort to emulate the integral theory of SUI [40], transabdominal transection of the pubourethral ligament (PUL) has been performed in rats [20[•]]. PUL injury produces a drop in LPP comparable to that of bilateral PNT up to 28 days after injury [20[•]]. Histologic studies confirm failure of the ligament to heal 4 weeks after injury, but insights into the neurologic aspects of this model have yet to be elicited.

Models simulating direct urethral damage

Some methods have utilized direct damage to the urethral sphincter to produce intrinsic sphincter deficiency as a durable model of SUI.

Periurethral cauterization

To replicate intrinsic sphincter deficiency in humans, Chermansky *et al.* [21] described electrocautery of the tissues directly lateral to the mid-urethra through an abdominal approach. Their model produced a drop in LPP 2 weeks after injury that was sustained for up to 16 weeks without concomitant changes in bladder function [21]. In addition to striated muscle damage, histology at 6 weeks showed nearly absent neuronal staining compared with uninjured controls, suggesting that marked distal neurogenic injury results from cauterization of the lateral periurethral areas [21].

Urethral sphincterectomy

A canine model of urethral sphincterectomy has been described, in which removal of approximately 25% of the urethral striated and smooth muscle was performed [41*]. Assessment of urethral pressure profilometry (UPP) and the urethral stress profile (USP) showed that decreased urethral resistance persisted for 7 months without recovery [41*]. Furthermore, in-vivo pudendal nerve stimulation produced sphincter contraction and increased urethral pressure, but, compared with uninjured controls, the response was significantly reduced in sphincterectomized dogs.

Botulinum toxin

Botulinum toxin – a potent neurotoxin that blocks the release of acetylcholine from axonal terminals – is utilized clinically via direct EUS injection to treat detrusor external sphincter dyssynergia from spinal cord injury [42]. In rats, botulinum toxin creates a pharmacologic denervation of the EUS with periurethral injection [43]. LPP reduction results 2 weeks after injection and is associated with smooth and striated muscle atrophy. Complete functional recovery, according to LPP, occurs 6 weeks after injury, making this a minimally traumatic and reversible model of SUI.

Animal model summary

Vaginal distension, PNC, and the dual-injury model emulate the damage that occurs during vaginal childbirth, but the injuries are recoverable. Vaginal distension causes direct tissue damage and distal neurologic injury, whereas PNC results in a proximal denervation followed by neuro-regeneration. PNT is a more severe, durable, and non-recoverable model, but is less physiologic. Urethrolisis and pubourethral ligament injury disrupt the native support of the urethra, resulting in a durable loss of urethral resistance. Direct injury to the urethra with electrocautery also produces a durable loss of urethral resistance and, like urethrolisis, shows evidence of distal denervation injury in addition to tissue damage. Sphincterectomy produces a severe and nonrecoverable muscular injury. Finally, botulinum toxin is a minimally traumatic, pharmacologic, and reversible model of SUI.

Conclusion

SUI is a common problem in women, with a complicated and multifactorial cause. The importance of vaginal childbirth injury in the predisposition to SUI is well known, and likely involves neurologic, muscular, and supportive tissue damage. Animal models of SUI replicate pudendal nerve injury as observed in women and the neurologic effects of indirect pelvic floor injuries. Animal model investigations are beginning to elucidate the neurologic and molecular mechanisms of the recovery of continence. Further research into the pathophysiology of childbirth injury and the promotion of continence recovery hold significant potential to benefit women's health.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 434–435).

1. Haylen BT, de Ridder D, Freeman RM, et al. An international urogynecological association/ international continence society joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodynam*. 2010; 49:4–20.
2. Milsom I. Lower urinary tract symptoms in women. *Curr Opin Urol*. 2009; 19:337–341. [PubMed: 19444118]
3. Hannestad YS, Rortveit G, Sandvik H, et al. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. *Epidemiology of Incontinence in the County of Nord-Trøndelag*. *J Clin Epidemiol*. 2000; 53:1150–1157. [PubMed: 11106889]
4. Richter HE, Burgio KL, Brubaker L, et al. Factors associated with incontinence frequency in a surgical cohort of stress incontinent women. *Am J Obstet Gynecol*. 2005; 193:2088–2093. [PubMed: 16325621]
5. Gregory W, Nygaard I. Childbirth and pelvic floor disorders. *Clin Obstet Gynecol*. 2004; 47:394–403. [PubMed: 15166863]
6. Tunn R, Goldammer K, Neymeyer J, et al. MRI morphology of the levator ani muscle, endopelvic fascia, and urethra in women with stress urinary incontinence. *Eur J Obstet Gynecol Rep Biol*. 2006; 126:239–245.
7. Snooks SJ, Swash M, Henry MM, Setchell M. Risk factors in childbirth causing damage to the pelvic floor innervation. *Int J Colorectal Dis*. 1986; 1:20–24. [PubMed: 3598309]
8. Lien KC, Morgan DM, Delancey JO, Ashton-Miller JA. Pudendal nerve stretch during vaginal birth: a 3D computer simulation. *Am J Obstet Gynecol*. 2005; 192:1669–1676. [PubMed: 15902175]
9. Diao E, Andrews A, Diao J. Animal models of peripheral nerve injury. *Oper Tech Orthop*. 2004; 14:153–162.
10. Dolan LM, Hosker GL, Mallett VT, et al. Stress incontinence and pelvic floor neurophysiology 15 years after the first delivery. *BJOG*. 2003; 110:1107–1114. [PubMed: 14664882]
11. Allen RE, Hosker GL, Smith AR, Warrell DW. Pelvic floor damage and childbirth: a neurophysiological study. *Br J Obstet Gynaecol*. 1990; 97:770–779. [PubMed: 2242361]
12. Snooks SJ, Swash M, Mathers SE, Henry MM. Effect of vaginal delivery on the pelvic floor: a 5-year follow-up. *Br J Surg*. 1990; 77:1358–1360. [PubMed: 2276018]
13. Cannon TW, Damaser MS. Effects of anesthesia on cystometry and leak point pressure of the female rat. *Life Sci*. 2001; 69:1193–1202. [PubMed: 11508351]
14. Ashton-Miller JA, DeLancey JO. Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci*. 2007; 1101:266–296. [PubMed: 17416924]
15. Lin AS, Carrier S, Morgan DM, Lue TF. Effect of simulated birth trauma on the urinary continence mechanism in the rat. *Urology*. 1998; 52:143–151. [PubMed: 9671889]
16. Bernabe J, Julia-Guilloteau V, Denys P, et al. Peripheral neural lesion-induced stress urinary incontinence in anaesthetized female cats. *BJU Int*. 2008; 102:1162–1167. [PubMed: 18549429]
17. Cannon TW, Wojcik EM, Ferguson CL, et al. Effects of vaginal distension on urethral anatomy and function. *BJU Int*. 2002; 90:403–407. [PubMed: 12175397]
18. Damaser MS, Whitbeck C, Chichester P, Levin RM. Effect of vaginal distension on blood flow and hypoxia of urogenital organs of the female rat. *J Appl Physiol*. 2005; 98:1884–1890. [PubMed: 15591288]
- 19••. Lin YH, Liu G, Li M, et al. Recovery of continence function following simulated birth trauma involves repair of muscle and nerves in the urethra in the female mouse. *Eur Urol*. 2010; 57:506–512. This experiment replicates the vaginal distension model in the mouse and demonstrates urethral evidence of denervation injury following vaginal distension. [PubMed: 19346061]
- 20•. Kefer JC, Liu G, Daneshgari F. Pubo-urethral ligament injury causes long-term stress urinary incontinence in female rats: an animal model of the integral theory. *J Urol*. 2009; 181:397–400. This novel rat model of the integral theory demonstrates that pubourethral ligament transection reduces LPP as much as bilateral PNT, with results that are durable at 4 weeks. [PubMed: 19010492]
21. Chermansky CJ, Cannon TW, Torimoto K, et al. A model of intrinsic sphincteric deficiency in the rat: electrocauterization. *Neurourol Urodyn*. 2004; 23:166–171. [PubMed: 14983430]

22. Kamo I, Cannon TW, Conway DA, et al. The role of bladder-to-urethral reflexes in urinary continence mechanisms in rats. *Am J Physiol Renal Physiol*. 2004; 287:F434–F441. [PubMed: 15113743]
23. Conway DA, Kamo I, Yoshimura N, et al. Comparison of leak point pressure methods in an animal model of stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*. 2005; 16:359–363. [PubMed: 16132162]
24. 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. [PubMed: 14624934]
25. Kamo I, Hashimoto T. Involvement of reflex urethral closure mechanisms in urethral resistance under momentary stress condition induced by electrical stimulation of rat abdomen. *Am J Physiol Renal Physiol*. 2007; 293:F920–F926. [PubMed: 17626152]
26. Resplande J, Gholami SS, Graziottin TM, et al. Long-term effect of ovariectomy and simulated birth trauma on the lower urinary tract of female rats. *J Urol*. 2002; 168:323–330. [PubMed: 12050564]
27. Rodriguez LV, Chen S, Jack GS, et al. New objective measures to quantify stress urinary incontinence in a novel durable animal model of intrinsic sphincter deficiency. *Am J Physiol Regul Integr Comp Physiol*. 2005; 288:R1332–R1338. [PubMed: 15650117]
28. 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 Int*. 2001; 88:771–775. [PubMed: 11890252]
29. Rempen A, Kraus M. Measurement of head compression during labor: preliminary results. *J Perinat Med*. 1991; 19:115–120. [PubMed: 1870048]
30. Pan HQ, Kerns JM, Lin DL, et al. Increased duration of simulated childbirth injuries results in increased time to recovery. *Am J Physiol Regul Integr Comp Physiol*. 2007; 292:R1738–R1744. [PubMed: 17204590]
31. Wood HM, Kuang M, Woo L, et al. Cytokine expression after vaginal distention of different durations in virgin Sprague–Dawley rats. *J Urol*. 2008; 180:753–759. [PubMed: 18554634]
- 32••. Woo LL, Hijaz A, Pan HQ, et al. Simulated childbirth injuries in an inbred rat strain. *Neurourol Urodynam*. 2009; 28:356–361. This article replicates the vaginal distension model from an outbred strain (Sprague–Dawley rats) in an inbred strain (Lewis rats), which has important uses for trials of stem-cell therapies for SUI. Similarly to prior research, this study demonstrates a marked increase in MCP-3 (a stem-cell homing cytokine) expression after vaginal distension.
33. Zhang J, Luo X, Xian C, et al. Endogenous BDNF is required for myelination and regeneration of injured sciatic nerve in rodents. *Eur J Neurosci*. 2000; 12:4171–4180. [PubMed: 11122329]
- 34••. Pan HQ, Kerns JM, Lin DL, et al. Dual simulated childbirth injury delays anatomic recovery. *Am J Physiol Renal Physiol*. 2009; 296:F277–F283. A study of the dual injury model (vaginal distension + PNC) which concludes that, although BDNF is important for neuroregeneration after injury, its expression is blunted by the addition of vaginal distension to the PNC injury. [PubMed: 19091786]
35. Damaser MS, Samplaski MK, Parikh M, et al. Time course of neuroanatomical and functional recovery after bilateral pudendal nerve injury in female rats. *Am J Physiol Renal Physiol*. 2007; 293:F1614–F1621. [PubMed: 17728381]
- 36••. Jiang HH, Pan HQ, Gustilo-Ashby MA, et al. Dual simulated childbirth injuries result in slowed recovery of pudendal nerve and urethral function. *Neurourol Urodyn*. 2009; 28:229–235. This assessment of the dual injury model incorporates PNMBP and EMG to measure pudendal nerve and EUS activity after injury and concludes that dual injury produces slower recovery than either injury alone. PNMBP is normal 4 days after vaginal distension, whereas EMG is not, indicating that neurologic injury occurs distal in vaginal distension. [PubMed: 18973146]
37. Kong W, Lin D, Kinley B, et al. Urethral neuromuscular injury following simulated childbirth injury in a rat model. *Neurourol Urodyn*. 2009; 28:597–598.
- 38••. Jiang HH, Gustilo-Ashby AM, Salcedo LB, et al. Electrophysiological function during voiding after simulated childbirth injuries. *Exp Neurol*. 2009; 215:342–348. This study combines the use of functional PNMBP and EMG assessments with histology following single-injury and dual-

- injury models to demonstrate that, despite recovery of LPP, neuromuscular regeneration and histologic recovery are still ongoing. [PubMed: 19056383]
39. Natale F, La Penna C, Saltari M, et al. Voiding dysfunction after antiincontinence surgery. *Minerva Ginecol.* 2009; 61:167–172. [PubMed: 19255563]
40. Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. *Acta Obstet Gynecol Scand Suppl.* 1990; 153:7–31. [PubMed: 2093278]
41. Eberli D, Andersson KE, Yoo JJ, Atala A. A canine model of irreversible urethral sphincter insufficiency. *BJU Int.* 2009; 103:248–253. The authors create a severe and durable model of SUI by removing 25% of the EUS in dogs. [PubMed: 18782310]
42. Chen SL, Bih LI, Huang YH, et al. Effect of single botulinum toxin A injection to the external urethral sphincter for treating detrusor external sphincter dyssynergia in spinal cord injury. *J Rehabil Med.* 2008; 40:744–748. [PubMed: 18843427]
43. Takahashi S, Chen Q, Ogushi T, et al. Periurethral injection of sustained release basic fibroblast growth factor improves sphincteric contractility of the rat urethra denervated by botulinum-a toxin. *J Urol.* 2006; 176:819–823. [PubMed: 16813954]