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Maybe it's nerves: Common pathway may explain pain

New studies also shed light on transvaginal ultrasound, laparoscopic excision, adhesions, hysterectomy, drug therapy.

Disruption of the inferior hypogastric nervous plexus during childbirth may result in reinnervation changes that cause visceral pain years later. The nerve injury theory would explain chronic pain after surgery, as well as the frequent co-involvement of urinary, gastrointestinal, and gynecologic organs in a common pelvic pain syndrome, since these organs share nerve pathways.



Many gynecologists now recognize that surgery is of little benefit in the initial diagnosis and treatment of the syndrome of chronic pelvic pain, but effective alternatives have not been well established either. Within the last year, however, new research has given us a better understanding of its causes, evaluation, and management. This Update discusses new findings on the following patient care issues:

- How a **common nerve pathway** may affect chronic pelvic pain patterns
- **Transvaginal ultrasound** in the evaluation of acute versus chronic pelvic pain
- The **placebo effect of surgery**
- What we can and cannot expect from **endometriosis resection**
- The role of **adhesions** in pain
- Limits of **hysterectomy**
- **Medical therapy**

Any nerve plexus injury may lead to pain

Quinn M. Obstetric denervation–gynaecological reinnervation: disruption of the inferior hypogastric plexus in childbirth as a source of gynaecological symptoms. Med Hypoth. 2004;63:390–393.

When we fit together the pieces of the chronic pelvic pain puzzle, a picture emerges that suggests the pelvic organs are connected functionally, not just by

anatomical proximity. Recent commercial promotion of drugs for diseases of the bladder and bowel has raised our awareness of interstitial cystitis and irritable bowel syndrome as factors in chronic pelvic pain, and we recognize that bowel and bladder symptoms often accompany gynecologic symptoms, such as dysmenorrhea and vulvodynia. Now, a hypothesis introduced by Martin Quinn suggests dis-

ruption of the inferior hypogastric nervous plexus during childbirth may result in reinnervation changes that cause visceral pain years later. He found collateral nerve-sprouting and a chaotic distribution of nerve fibers when special stains were used on surgical specimens.

According to this hypothesis:

- **Cesarean section is not the answer** to this childbirth-related injury, because cesarean section injures the nerve plexus.
- **Hysterectomy would be effective** for chronic pain only if abnormal nerve regeneration is restricted to the uterus.

Although Quinn focused on obstetric injury, it follows that other injury to the nerve plexus could have the same consequences; for example, gynecologic surgery (eg, laparoscopy), pelvic infection, or automobile trauma.

DIAGNOSIS

Ultrasound is more useful for acute than chronic pain

Okaro E, Valentin L. The role of ultrasound in the management of women with acute and chronic pelvic pain. Best Pract Res Clin Obstet Gynaecol. 2004;18:105-123.

Clinicians are taught that a good history and physical examination are the most important diagnostic tools in evaluating symptoms, but we often use imaging studies as well, including routine transvaginal ultrasound in the evaluation of pelvic pain. This analysis of published studies identified transvaginal ultrasound as an extension of the bimanual exam, but observed its greatest utility for acute rather than chronic pelvic pain. In chronic pelvic pain, laparoscopic findings, if abnormal, commonly include endometriosis and adhesions—for which transvaginal ultrasound is not very useful unless there is fixation or enlargement of the ovary.

This review describes use of ultrasound for identification of heterogeneous

myometrial echotexture, asymmetric uterine enlargement, and subendometrial cysts as features of adenomyosis, and reports a positive predictive value of 68% to 86% in published series.

SURGERY

Excision can be effective—so can sham surgery

Abbott J, Hawe J, Hunter D, Holmes M, Finn P, Garry R. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. Fertil Steril. 2004;82:878-884.

Some gynecologists still choose surgery as a first-line treatment, although a landmark randomized trial published 14 years ago proved that a nonsurgical approach more effectively resolves chronic pelvic pain symptoms.¹ The enthusiasm for surgery is highest when endometriosis is suspected, and some gynecologists still believe that the only adequate treatment is physical removal or destruction of implants.

Pain relief has been attributed to laparoscopic treatment of endometriosis, but cause-and-effect is uncertain, in part because of confounding factors.

For example, in a report on outcomes after ablative therapy for stage 3 or 4 endometriosis with endometriotic cysts, Jones and Sutton² considered surgery successful because 87.7% of subjects were satisfied 1 year later. This interpretation can be questioned, however, given that patients who did not want to conceive were treated with oral contraceptives or gonadotropin-releasing hormone analog after surgery. The extent to which symptoms responded to the medication rather than the surgery is not known.

Also unknown is the extent to which symptoms respond to the placebo effect of surgery. Sutton and colleagues had previously shown that pain relief 3 months after laser laparoscopy was no greater than after sham surgery,³ but by 6

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Cesarean section injures the nerve plexus, and therefore does not avert childbirth-related nerve trauma

months, pain relief in the sham surgery group was not sustained, and was lower than in the real surgery group.

The new study by Abbott et al re-addressed the placebo effect of surgery by randomizing 39 women with pain and visible endometriosis implants to either diagnostic laparoscopy or laparoscopic excision of endometriosis. Six months after the surgery, the women had a second laparoscopic procedure during which the extent of endometriosis was reevaluated and visible disease was resected. In other words, all women had resection of endometriosis, although in half of the subjects, the resection was preceded by a sham operation.

Six months after the first operation, 80% of the resection group said they were improved, compared to 32% of the sham surgery group. Six months after the second operation, 83% of those who initially had sham surgery were improved.

This study shows that surgical resection can be effective in reducing pain associated with visible endometriosis, but there are 2 important additional findings:

- The placebo response of 32% is considerable and not to be ignored.
- Despite aggressive excisional surgery with its risks of major organ injury, up to 20% of subjects did not improve.

Furthermore, this study did not explore duration of response to surgery, nor compare surgical to nonsurgical therapy.

Is adhesiolysis helpful or not?

Hammoud A, Gago A, Diamond MP. Adhesions in patients with chronic pelvic pain: a role for adhesiolysis? *Fertil Steril*. 2004;82:1483-1491.

Adhesions may be blamed for chronic pelvic pain, although randomized trials have shown adhesiolysis no more effective than sham surgery.^{4,5} Hammoud et al hypothesized that adhesions cause pain when they distort normal anatomy and

pull on peritoneum, but stress that this idea has not been validated.

Their study found substantial evidence against the theory that adhesions cause pain, and suggests that pain and adhesions may both be due to an underlying process such as endometriosis.

They also review the evidence on the important complications that may occur with attempted surgical adhesiolysis.

Hysterectomy less helpful with preop depression

Hartmann KE, Ma C, Lamvu GM, Langenberg PW, Steege JF, Kjerulff KH. Quality of life and sexual function after hysterectomy in women with preoperative pain and depression. *Obstet Gynecol*. 2004;104:701-709.

Some gynecologists use removal of the uterus as the definitive treatment for chronic pain, although no controlled studies have examined the effectiveness of this operation compared to nonsurgical treatments. Hartmann et al evaluated quality of life and sexual function after hysterectomy in women who had pain, depression, or both pain and depression prior to surgery.

Results were compared between these groups and with women who had neither pain nor depression before surgery. Women with both pain and depression were more likely to have impaired quality of life after hysterectomy than were women with pain or depression alone or women with neither pain nor depression.

Two years later, pelvic pain was still troubling 19.4% of women with preoperative depression and pain, and only 9.3% of women with preoperative pain only.

Hysterectomy led to improvement in many quality of life measures and sexual function in women with pain, depression, or both. The authors concluded, "Overall we do not do harm when we perform hysterectomy for these complex patients."

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The 32% placebo response to surgery is not to be ignored —nor is the 20% lack of improvement with aggressive excisional surgery

That conclusion, however, fails to consider surgical complications, time lost from work or other activities, or monetary costs, which were not evaluated.

There was no nonsurgical comparison group, and the authors point out that their study did not address the possibility that nonsurgical treatments may be as effective or more effective than hysterectomy.

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MEDICAL THERAPY

Letrozole for endometriosis?

Ailawadi RK, Jobanputra S, Kataria M, Gurates B, Bulun SE. *Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil Steril.* 2004;81:290-296.

The discovery that endometriosis implants may contain the aromatase enzyme prompted consideration of aromatase inhibitors as a nonsurgical treatment for endometriosis. These agents, which prevent conversion of androgens to estrogens, are used in the management of breast cancer.

This pilot study evaluated the use of the aromatase inhibitor letrozole in 10

women in whom medical and surgical therapy for endometriosis had failed. Add-back therapy with norethindrone acetate was given to prevent the decrease in bone mineral density that might have occurred with letrozole alone. In 9 of the 10 women, pain decreased over the 6 months of the study.

This encouraging result suggests that larger trials with control subjects and longer follow-up will be worthwhile.

Recommendation: Use GnRH agonist

Nasir L, Bope ET. *Management of pelvic pain from dysmenorrhea or endometriosis. J Am Board Fam Pract.* 2004;17:S43-S47.

Recommendations from the Family Practice Pain Education Project published at the end of 2004 support use of nonsurgical therapies for endometriosis, based in part on the findings of Ling et al,¹ which demonstrated the effectiveness of empirical therapy.

ACOG agrees

That recommendation is similar to the nonsurgical approach to chronic pelvic pain recommended in 1999 in an ACOG Practice Bulletin²:

“Therapy with a GnRH agonist is an appropriate approach to the management of women with chronic pelvic pain, even in the absence of surgical confirmation of endometriosis, provided that a detailed initial evaluation fails to demonstrate some other cause of pelvic pain.” ■

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Empirical therapy with a GnRH agonist is endorsed by the Family Practice Pain Education Project and ACOG