Chronic Pain Secondary to Childbirth

Does It Exist?

PERSISTENT pain after operative procedures such as inguinal hernia repair, breast surgery, and coronary artery bypass surgery occurs in as many as 10–50% of individuals.[1] Kehlet *et al.*[1] assert that chronic postoperative pain results from either dysregulation of inflammation pathways leading to ongoing inflammation or neuropathic pain induced by surgical trauma. Arguably, childbirth is associated with inflammatory changes and trauma in a large proportion of the world's population.[2] Whether neuropathic changes are induced is unknown. In a 2010 review, Vermelis *et al.*[3] suggested that the incidence of chronic pain ranged from 4–10% after vaginal delivery and 6–18% after cesarean delivery. Thus, given the large number of potentially affected individuals, the development of chronic pelvic pain after childbirth[4] is of significant interest and concern.

"Understanding whether and how pregnancy or the puerperium protects against the development of posttraumatic chronic pain ..."

In this issue of ANESTHESIOLOGY, research teams led by Eisenach describe the results of two studies that directly and indirectly investigated childbirth pain.[4,5] The first article reports the results of a multicenter longitudinal cohort study of pain and depression after human childbirth.[4] The second study uses a rat model to investigate the potential protective effect of oxytocin on the development of neuropathic hypersensitivity.[5]

For the human study, the investigators recruited more than 2,500 women from two major U.S. institutions and two European institutions.[4] Study subjects were interviewed about chronic, pregnancy-associated, and acute postpartum pain within 36 h of delivery; scripted pain questionnaires were administered at 2-, 6-, and 12-months after delivery. Follow-up at the American sites was by phone; only those subjects who reported pain at 2 months were followed up at 6 months, and similarly, only those with pain at 6 months were followed-up at 12 months. Follow-up at the European sites was attempted by post, but the 6- and 12-month questionnaire return rates were very low (4% at 12 months); the follow-up rate at 2 months was not reported.[4,6] Iterative techniques were used to account for the missing American data (24%) whereas the European data were not analyzed due to the low response rate.

The investigators have previously reported a secondary analysis of the same data set with 2-month follow-up; severity of acute postpartum pain was predictive of pain and depression at 2 months (incidence approximately 10.5% and 11.2%, respectively), but mode of delivery was not.[6] In the current study, the investigators attempted to generate a predictive model of chronic pain and depression after childbirth, while taking into account the severity of acute postpartum pain. A model was generated for the presence of pain and depression at 2 months, but the low incidence of pain at 6 and 12 months precluded this exercise at these time periods.

The primary outcome of the study was defined as pain *which began at the time of labor and delivery* in a location, which could be ascribed to delivery (pelvis, perineum, abdomen).[4]The prevalence of pain was 1.2% (upper 95% CI) at 12 months (absolute number of 3). Although a history of pain and degree of tissue damage at delivery accounted for some of the variance in acute postpartum pain, these factors did not predict the presence of new pain attributable to delivery at 2 months.

Eisenach *et al.*[4] suggest that several aspects of the study results are surprising: (1) the low incidence of pain at 12-months as compared with that found in other studies of cesarean delivery; and (2) the lack of association of tissue damage and history of chronic pain with the presence of pain 2 months after delivery. Degree of tissue damage and history of chronic pain have been reported to be associated

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with the development of chronic pain in other, nonobstetric, postsurgical investigations.[1] Eisenach *et al.*[4] suggest that these findings can be explained by one of several mechanisms: either the degree of tissue damage that occurs during childbirth is too low to result in chronic pain, or there are protective biologic or psychosocial factors at play during pregnancy and/or the puerperium, which protects against the development of chronic pain. The former explanation seems unlikely, especially given the high incidence of cesarean delivery, a major operative procedure.

To investigate a potential mechanism for reduced pain sensitivity during pregnancy and/or the postnatal period, Gutierrez *et al.*[5] performed a second study using a rat model to test whether pregnancy or nursing affected the development of spinal nerve ligation-induced hypersensitivity to a mechanical stimulus. The authors hypothesized that physiologic changes in pregnancy and/or the puerperium may protect against the development of hypersensitivity, and that oxytocin may play a role in this protective effect.

In the preclinical study, spinal nerve ligation or a sham procedure was performed in pregnant rats either 1 week before delivery or on the day of delivery, and in nonpregnant control animals. Withdrawal of the hind limb to a mechanical stimulus was tested in the pregnant rats and before and after weaning postpartum. Testing was performed in the nonpregnant control group at an equivalent time point. Pregnant and nonpregnant animals developed equivalent hypersensitivity after spinal nerve ligation, which did not diverge until delivery. After delivery, the pregnant animals that remained with their pups partially recovered. To directly investigate the role of spinal oxytocin in altering the response to spinal nerve ligation, oxytocin, atosiban (an oxytocin receptor antagonist), and naloxone (an opioid receptor antagonist) were injected intrathecally 21 days after delivery in rats that had undergone spinal nerve ligation. Oxytocin reversed hypersensitivity, atosiban accentuated hypersensitivity, and naloxone was without effect. The authors sampled cerebral spinal fluid for oxytocin; it was present but was highly variable in the postpartum animals whose pups had not been weaned.

The findings from these two new studies are very intriguing but certainly bear scrutiny. The human study was initially large and multicentered, and prospectively addressed new childbirth pain after both cesarean and vaginal delivery after 1 year. However, the number of study subjects lost to follow-up was also large (close to 100% in the European centers). As such, long-term follow up was only accomplished in a much smaller cohort in only two centers. Study subjects were recruited from two institutions that provide excellent intrapartum and postpartum obstetric and obstetric anesthesia care, and most of the subjects received neuraxial analgesia or anesthesia, and presumably multimodal postpartum analgesia. This management may be important because type of anesthesia and quality of postoperative analgesia has been associated with the development of chronic pain.[1,7] The investigators were unable to develop models to identify factors associated with the development of chronic pain at 6 and 12 months due to the small number of subjects with pain. Only those subjects reporting pain on the previous assessment were followed up at the next assessment period; ideally, all study subjects would be assessed at each assessment period. It would be useful to validate the predictive model developed in this study in a separate group from the same or different institutions. Furthermore, the socioeconomic, racial, and cultural backgrounds of the study subjects were not described and were likely variable between institutions. These issues would also be important for consideration in future studies.

Postsurgical pain in other patient populations has been shown to have neuropathic characteristics, yet the small sample size and survey-based reporting do not allow for sure characterization of the chronic pain in the current study population as neuropathic. Inflammatory pain may differ from neuropathic pain with regard to risk factors, prevention, and treatment.[1]Although the authors concluded in both the previous report[6] and the current study[4] that mode of delivery was not associated with new delivery-associated pain at 2 months, all new pelvic/abdominal/perineal pain was included in this outcome. It is possible that development of chronic pain in specific locations (*e.g.*, scar pain, vaginal pain) does depend on the mode of delivery. Finally, the low incidence of chronic pain identified in this study differs markedly from that identified in other studies. For example, in an analysis of the *Listen to Mothers II* database, the incidence of cesarean incision pain that persisted for a minimum of 6 months was 17% in primiparous women,[8] and in a small Danish study, the incidence of postcesarean scar pain at 1 year was more than 12%.[9] The reasons for these differences are not clear, but may include differences in study design, specific outcome definitions and assessment techniques, study populations, and intrapartum analgesia/anesthesia management, among other factors. Thus, the findings of the current study are important, but should be confirmed in other populations with appropriate testing to identify neuropathic and ongoing inflammatory pain.

Similarly, the results of the animal study provide significant fodder for further research. The investigators used a rat model of surgically induced neuropathic pain. The authors began this study with the assumption that postpartum pain would be neuropathic in nature and thus used an animal model for neuropathic pain. This assumption must in itself be questioned as there is a clear role for inflammatory changes in the peripartum period[2] and dysregulation of inflammation in chronic pain.Therefore, it will also be important to study the impact of the postpartum period in a standard model for acute inflammatory pain. Nonetheless, these data suggest that exposure to oxytocin may ameliorate neuropathic pain in the setting of pregnancy and perhaps in other situations. As the authors acknowledge, although oxytocin is present in the spinal fluid, these studies were not designed to identify a spinal site of action.

The two studies reported in this issue provide important new information toward understanding the development of chronic pain after childbirth. Accurate estimation of the number of affected individuals and pain severity are clinically significant concerns because of the large population at risk. Understanding whether and how pregnancy or the puerperium protects against the development of posttraumatic chronic pain is important not only to women who give birth and their children, but may also provide therapeutic targets for future prevention and treatment of chronic pain in other populations.

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