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FACTFINDERS for PATIENT SAFETY: Preventing procedure-related complications: Epidural lipomatosis and postpartum steroid exposure

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A B S T R A C T

This series of FactFinders presents a brief summary of the evidence and outlines recommendations to improve our understanding and management of potential procedure-related complications.

Evidence in support of the following facts is presented. (1) *Epidural Steroid injections for Radicular Pain Due to Spinal Stenosis Caused by Lipomatosis* – There is low-level evidence of an association between epidural steroid injections (ESIs) and the development and/or worsening of spinal epidural lipomatosis (SEL). However, there is insufficient evidence to establish whether ESIs independently result in an increase in spinal stenosis with neurological compromise in individuals with pre-existing SEL. (2) *Steroid Exposure Postpartum* – There is no absolute contraindication to steroid injections based on postpartum or lactating status, but there may be disruption of both maternal and breastfed child hypothalamic-pituitary-adrenal (HPA) axis response to steroid administration. For the duration of breastfeeding, milk production may be affected after steroid exposure, and withholding breast milk produced for several hours after exposure minimizes infant exposure.

FACTFINDERS FOR PATIENT SAFETY:

Epidural Steroid injections for Radicular Pain Due to Spinal Stenosis Caused by Lipomatosis.

Ryan S. D'Souza, MD; George Christolias, MD; Eric K. Holder, MD; Haewon Lee, MD; Clark Smith, MD, MPH; and Jaymin Patel, MD on behalf of the International Pain and Spine Intervention Society's Patient Safety Committee.

MYTH: Epidural steroid injection is contraindicated in patients with spinal stenosis due to epidural lipomatosis.

FACT: There is low-level evidence of an association between epidural steroid injections (ESIs) and the development and/or worsening of spinal epidural lipomatosis (SEL). However, there is insufficient evidence to establish whether ESIs independently result in an increase in spinal stenosis with neurological compromise in individuals with pre-existing SEL.

Spinal epidural lipomatosis (SEL) is a condition of excess, non-encapsulated adipose tissue deposition circumferentially within the epidural space [1]. The etiology of SEL remains unclear; however, studies have highlighted four broad categories, which include: exogenous steroid administration, endogenous steroid hormonal disease, obesity, and idiopathic [1]. SEL can cause symptoms such as axial low back pain, radiculopathy, neurogenic claudication, myelopathy, or cauda equina syndrome, depending on its location and extent, while also being asymptomatic in many cases [1]. Spine magnetic resonance imaging (MRI) can identify the presence of SEL. Although well-defined and reproducible grading systems exist [2,3], they are utilized inconsistently in studies on this subject matter. There is no broadly accepted definition or cutoff measure to define SEL. Treatment includes reduction of exogenous steroid dose, treatment of underlying endocrinopathy, dietary changes, and surgical decompression/laminectomy in severe circumstances [4]. A literature review identified 49 cases of idiopathic SEL and 62 cases of secondary SEL treated with surgical decompression resulting

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in full recovery of symptoms in 60% of lumbar cases and 15–50% in cases involving the thoracic spine [5]. The authors did not report on the rate of surgical complications.

Systemic exogenous corticosteroid administration is the most common etiology of SEL [6]. Systemic corticosteroids stimulate glucocorticoid receptors within adipose tissue, which may result in the expansion of adipose tissue in the Cushingoid fat distribution and pre-existing epidural adipose tissue [6,7]. Conversely, local steroid administration, such as epidural steroid injections (ESIs), is not as clearly associated with the development of or increase in SEL. Thus, while ESI is a common treatment offered to patients with radicular pain secondary to disc herniation and degenerative spinal stenosis [8,9], it is unclear if this treatment is appropriate for patients with radicular pain primarily due to spinal stenosis caused by SEL.

Does ESI increase adipose deposition in the epidural space?

A total of four case reports [10–13], two case series [14,15], and three observational studies [16–18] comprising 861 patients discussed SEL after ESI administration. All studies reported the progression of SEL after ESI or an association between SEL and ESI. The largest study reviewed the MRIs of 28,902 patients and identified that the rate of SEL was 2.5% (731 patients) [18]. The authors reported that incidental SEL was present in 168 cases (0.6%), SEL with spine-related symptoms was present in 526 cases (1.8%), and symptomatology specific to SEL was present in 37 cases (0.1%). Multivariate logistic regression revealed that the most important risk factor associated with overall SEL (both incidental SEL detected on imaging and symptomatic SEL) was prior ESI (Odds Ratio [OR] 3.48, $p < 0.001$). This study also identified other risk factors associated with SEL, including older age, higher modified Charlson comorbidity index [19], male sex, African American race, and systemic corticosteroid use. A subgroup analysis stratified patients with incidental SEL, SEL with spine-related symptoms (*e.g.*, radiculopathy, neurogenic claudication, spinal cord compression), and symptomatic SEL with SEL-specific symptoms (*e.g.*, SEL responsible for symptoms). Multivariate logistic regression revealed that SEL with spine-related symptoms was associated with prior ESI (OR 3.96, $p < 0.001$), though no sub-analysis was performed to assess the association between prior ESI and patients with SEL-specific symptoms.

A case-control study compared 70 patients with SEL diagnosed by MRI and 34 randomly selected control patients [16]. This study defined SEL based on compression or distortion of the thecal sac and/or nerve sheath by lipoid on MRI T1 films. This study identified a strong correlation between the number of ESIs and radiographic evidence of worsening SEL. The absence of ESI delivery or a single ESI was not associated with the radiographic evidence of SEL. After three ESIs and four ESIs, the probability for radiographic evidence of SEL was 98% and 100%, respectively. Similarly, a cross-sectional study reported that among patients with SEL, 33% (17/52) had previously received an ESI [17]. There was no matched control group.

The findings from these observational studies are further substantiated by case reports [10–13] and case series [14,15] highlighting the progression of SEL with serial MRI imaging after ESI. In one case report, new numbness and dysesthesias developed in the lower extremity with new focal SEL causing thecal compression at the same spinal level where the ESI was previously performed [10]. In another case, serial MRIs revealed a circumferential increase in SEL after 13 ESI procedures were performed over a 5-year span, with subsequent resolution of SEL 7 months after cessation of steroid injections [11].

In summary, all included studies demonstrate either the development or progression of SEL after ESI. One such publication reported an association between a greater degree of SEL and the number of ESIs [16]. The level of evidence for these findings is low given the type of study design (retrospective observational studies and case reports/series), the presence of confounding variables that were not adjusted within observational studies, and sources of heterogeneity between studies. Causality cannot be established in the absence of prospective studies.

Does ESI worsen pain and neurological symptoms in patients with pre-existing SEL?

A total of five case series [14,15,20–22] and one case report [10] comprising 12 patients discussed pain severity and neurological symptoms after ESI administration in patients with pre-existing SEL. Favorable outcomes were reported in two case series [20,21]. In two patients with pre-existing SEL causing pain symptoms, there was an 80–85% improvement in pain intensity at 2 weeks after ESI with triamcinolone, and the neurological examination remained stable at follow-up appointments spanning 8–18 months [20]. Three patients with lumbosacral radiculopathy experienced a 50–75% decrease in pain scores and an improvement in pain disability index by 13–44 points after ESI with dexamethasone [21]. Both of these case series that reported favorable outcomes utilized the transforaminal approach when performing ESI [20,21], though the ability to extrapolate these implications is limited by a small sample size.

Two case series reported worse outcomes after ESI in patients with SEL [14,22]. Two patients with pre-existing SEL had a progression of neurological deficits less than 5 months after ESI [14]. Similarly, another case series highlighted a patient who had received 103 ESI procedures over a 12-year period and abruptly developed T10 paraplegia due to spinal cord compression and required T10-L2 laminectomy and decompression with removal of epidural fat [22]. Notably, the number of ESIs administered in this case series was more than double the maximum limit for the number of ESIs recommended by most society guidelines during that period of time [23].

Equivocal outcomes were reported in one case series [15] and a case report [10]. One patient with radicular pain symptoms obtained short-term benefit after three ESIs; serial MRI revealed progression to borderline grade II SEL without worsening neurological symptoms associated with spinal stenosis [15].

Conclusion and recommendations

1) There are limited data from observational studies and case reports/case series investigating ESIs in patients with SEL [24]. Prospective and appropriately-powered studies are needed to establish if there is a causal relation between ESI and both radiographic and symptomatic progression of SEL.
2) Low-level evidence indicates an association between SEL documented on MRI and a history of prior ESI. Physicians may consider advising patients about the potential for an increase in SEL radiographically and an increase in spinal stenosis-related symptoms due to the progression of SEL after receiving an ESI.
3) The number of ESIs performed and the dosage of corticosteroid utilized before the onset or progression of SEL is highly variable. SEL has been reported even after one ESI [14]. Low-level evidence demonstrates a correlation between the number of ESIs performed and the subsequent development of SEL.
4) Some case series that included patients with pre-existing SEL report modest, short-term improvement in pain severity and disability following ESI. In contrast, others report worsening neurological deficits.
5) Several studies do not clearly describe the ESI approach (interlaminar versus transforaminal) utilized in their patient cohort [24]. Two case series ($n = 5$) utilized a transforaminal approach for managing symptomatic radiculopathy due to SEL, demonstrating improved pain severity and disability [20,21]. Additional studies evaluating the ESI approach and outcomes are needed.
6) In the referenced publications, high doses of corticosteroid were commonly administered, exceeding currently recommended doses in contemporary clinical practice [25]. There are no studies specifically

assessing corticosteroid type or dose utilized in ESI as it relates to the initiation or progression of SEL.

FACTFINDERS FOR PATIENT SAFETY.

Steroid Exposure Postpartum.

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Myth: Steroid administration via spinal injections is contraindicated in postpartum patients, especially if breastfeeding.

Fact: There is no absolute contraindication to steroid injections based on postpartum or lactating status, but there may be disruption of both maternal and breastfed child hypothalamic-pituitary-adrenal (HPA) axis response to steroid administration. For the duration of breastfeeding, milk production may be affected after steroid exposure, and withholding breast milk produced for several hours after exposure minimizes infant exposure.

The postpartum period is defined as the period between delivery of the conceptus to when maternal physiology returns to a nonpregnant state [26]. The duration of this period is debatable and ranges from 24 h (considered the acute phase) up to months after delivery or until lactation stops [27]. In the postpartum period, there are maternal physiological changes, including changes in hormonal regulation both separate from and related to lactation [26]. Studies have suggested that women may be particularly susceptible to back pain in this period, with a point prevalence of 67% [28], possibly as a result of pregnancy-related weight changes, alteration of posture, as well as physical demands related to childrearing [28,29]. Consequently, postpartum women may be regarded as candidates for interventional procedures which may incorporate glucocorticoid therapeutic agents given their higher incidence of back pain compared to the general population in a similar age range. This may raise safety concerns about steroid exposure in postpartum women as steroids may disrupt the already altered HPA axis, affect breast milk production, and be secreted in the breast milk from lactating individuals after steroid exposure with ensuing potential adverse effects on the newborn [30].

Changes in maternal response to steroid administration in the postpartum period

Systemic side effects of steroid exposure include transient hyperglycemia, hypertension, fluid retention, altered hematopoietic response, psychiatric effects, and Cushing's Syndrome [31] as previously summarized by published FactFinders on the effects of steroid exposure during spine injections [32,33]. Except for hyperglycemia, which originates from directly reducing the action of insulin and increasing the hepatic release of glucose, many of these side effects stem from changes in the HPA axis [34]. In the postpartum period, the HPA axis undergoes dramatic changes, which may impact the side effects profile experienced by exogenous glucocorticoid administration when compared to non-postpartum patients after steroid injections [35]. In pregnancy, there is an increase in serum cortisol levels partly due to estrogen stimulation of the corticosteroid-binding globulin with a rise in bioavailable cortisol levels [35]. In the postpartum period, maternal plasma cortisol levels eventually fall, and the HPA axis returns to its nonpregnant state [36]. Suppression of corticotropin-releasing hormone following pregnancy is evident at 3 weeks and 6 weeks and normalizes by 12 weeks [37]. Lactating women may demonstrate longer disturbances as other studies have shown that prolactin, typically elevated during lactation, may blunt HPA responses to stress [38]. Overall, data are lacking, but postpartum women may have altered systemic physiologic responses to exogenous steroids. Some of this response is mediated by altered relative estrogen vs. prolactin levels [39], which may result in an amplified systemic side effect profile that differs from non-pregnant individuals.

Steroid secretion in breast milk after exogenous administration

The American College of Obstetricians and Gynecologists Committee Opinion categorized glucocorticoids as low-risk in terms of teratogenicity and states they are "compatible" with breastfeeding [40]. A summary from the British Society of Rheumatology and others classify corticosteroids as "compatible with pregnancy and breastfeeding [41]." However, as steroids can be transmitted in breast milk [42], historically, some have advised withholding breast milk produced from lactating women who receive spinal steroid injections [43]. The best-studied steroid in lactating patients is intravenous methylprednisolone [44]. The quantity of methylprednisolone secreted in breast milk is very low, and no adverse reactions in breastfed infants have been reported in the literature [44]. A study of lactating individuals with multiple sclerosis was conducted in which individuals received 1 g of methylprednisolone intravenously. Breast milk samples were taken 1, 2, 4, 8, and 12 h after exposure. Levels of methylprednisolone in breast milk peaked at 1 h after infusion and averaged 1.24 mg/L before leveling off to 0.04 mg/L by 8 h and 0.01 mg/L at 12 h [45,46]. By comparison, normal breast milk cortisol is less than 0.02 mg/L [18]. The authors of this study recommended interrupting lactation or a "pump-and-dump" strategy within 4 h of infusion [46], although other groups have advised a shorter interruption of only 2 h. Note that the systemic effects of locally injected corticosteroids are dose-related [47] and 1 g of methylprednisolone was administered intravenously, which would likely yield more systemic effects than a localized epidural or joint injection, and 1 g is about 25 times the dose of an epidural steroid injection. Studies on peak serum concentration after steroid injections in the spine are lacking, but one study suggested that peak serum concentration of triamcinolone following intra-articular facet joint injections occurred within 24 h with a serum triamcinolone level of 3.6 ng/mL [48]. Such detailed analyses of breast milk secretion after steroid exposure have not been performed for other steroids such as betamethasone [49], triamcinolone [50], and dexamethasone [51]. It is unclear whether it is necessary to withhold breast milk produced from lactating women who receive spinal steroid injections.

Effects of maternal steroid administration on lactation

Endogenous steroids are involved in breast milk initiation and maintenance of production. Animal studies have shown that exogenous glucocorticoid steroid administration can diminish milk production and ejection [52]. In case reports, a lactating woman who was 6 weeks postpartum and primarily breastfeeding received an injection of 24 mg of methylprednisolone for De Quervain's tenosynovitis and experienced a temporary cessation of breast milk production. Production resumed spontaneously 36 h later and normalized 90 h after the injection [52]. In another case report, a high-dose injection of 80–120 mg triamcinolone injected into cervical and thoracic regions epidurally resulted in significant breast milk reduction in a patient who had established lactation [53]. Interestingly, in this same woman, a prior lower dose (5.7 mg) betamethasone injection into the shoulder for bursitis did not affect milk production [53]. Whether the difference is secondary to the dose or somehow a cumulative effect is unknown.

Effects in breastfed infants

The Drugs and Lactation Database (LactMed) provided by the National Institute of Health currently reports that for methylprednisolone: "amounts of methylprednisolone [secreted] in breast milk are very low, and no adverse reactions in breastfed infants have been reported" [42]. However, it should be acknowledged that there are minimal published data about the effects on breastfed infants from maternal steroid exposure to methylprednisolone or other exogenous corticosteroid administration. A prior retrospective analysis demonstrated a reduction in infant weight, length, and head circumference with increased human milk

glucocorticoid levels, mostly as a result of betamethasone administration as two 12-mg intramuscular injections 24 h apart to the mother [54]. This study reported preliminary evidence that supports a possible association between glucocorticoid levels in ingested milk and infant adiposity and head circumference during the first year of life. However, several case reports and series on maternal systemic steroid exposure (oral or intravenous) demonstrated no changes in these measures in breastfed infants. First, in a population of 16 postpartum females with multiple sclerosis who received intravenous steroids and did not breastfeed for 4 h after a systemic steroid dose, no adverse effects were observed in infants between 3 and 12 months follow-up [55]. Second, in a study of infants breastfed by mothers receiving methylprednisolone intravenously after only withholding milk 2 h after infusion, the infants displayed no adverse effects up to 24 months with normal weight, height, and developmental milestones [50]. Finally, in a single case of a mother with rheumatoid arthritis treated with oral methylprednisolone daily plus intermittent corticosteroid injections while breastfeeding her infant, there was normal growth, psychomotor development, and laboratory data in the baby at 9 months of age [56]. These case reports and series highlight the possible safety of maternal systemic steroids on the breastfeeding neonate, but additional high-quality, well-powered, and long-term studies are warranted to confirm the accuracy of their conclusions.

Conclusion

In the immediate and postpartum periods, there are significant changes to the HPA axis. Spinal corticosteroid injection during the postpartum period may be a factor that results in three potential adverse effects: prolongation of maternal HPA axis suppression, interference with infant growth and development, and disruption of lactation.

Recommendations

- Inform women in the postpartum and lactating period of the possible additional adverse effects of systemically absorbed corticosteroid.
- Systemic effects of locally injected corticosteroids are dose-related, and use of the lowest effective dose is recommended in all patients, including postpartum patients.
- For lactating patients, discuss the potential risks of corticosteroid administration for the breastfed infant, possibly associated with disrupted infant growth and development. A 'pump and dump' strategy may be considered after injectable corticosteroid administration, but direct evidence is lacking to support this practice.
- Inform lactating patients that steroid exposure has been associated with temporary effects on milk production in certain individuals. It is unknown how frequently this occurs.

Conflicts of interest

None.

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Declaration of competing interest

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