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Spinal Cord Stimulation and Intrathecal Drug Delivery System Therapy in a Pregnant Patient with Complex Regional Pain Syndrome Type II: A Case Report

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Background: Complex Regional Pain Syndrome (CRPS) is a difficult-to-treat chronic pain condition. When indicated, spinal cord stimulator (SCS) therapy can serve as a solution. Rarely, intrathecal drug delivery system (IDDS) can be used with SCS to enhance analgesia. Given women's predisposition towards CRPS, there may be an increasing co-existence of pregnancy and CRPS.

Case Report: A pregnant woman presented with right lower extremity pain due to CRPS type II. Here, we present the first case of a woman who continued SCS and IDDS therapies throughout pregnancy. She had an uncomplicated pregnancy, labor, and delivery. The baby achieved all developmental milestones at one year.

Conclusion: Further research on the safety of SCS and IDDS during pregnancy is required to determine their effects on the mother and fetus. Until then, the decision to continue these therapies should be considered individually and with close collaboration among the patient, obstetrics, and pain management teams.

Key words: Pain management, pregnancy, refractory complex regional pain syndrome, CRPS, intrathecal pump therapy, spinal cord simulation

BACKGROUND

Complex regional pain syndrome (CRPS) is a challenging chronic pain syndrome that typically affects the extremities in a nondermatomal distribution. It is characterized by pain disproportionate to any inciting event, with associated allodynia or hyperesthesia, skin color or temperature changes, edema or sweating changes, motor dysfunction, and trophic changes (1,2). CRPS is further classified into CRPS type I and CRPS type II, with the latter occurring in the presence of a nerve injury and previously called causalgia (3). While the pathogenesis leading to this debilitating condition is not yet fully understood, it is suspected that inflammatory mediators, central and peripheral nervous system sensitization, sympathetic dysfunction, psychological factors, autoimmunity, and genetic components may play a role following an inciting event (4).

Demographically, being a woman and being elderly are

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risk factors for CRPS, with women being 2 to 4 times as likely to develop this condition; reported peak incidences occur at age 40 (5-7). In light of the increasing mean age of mothers at first birth, it is imperative to examine how to optimally manage this condition during pregnancy (8).

Treating CRPS requires a multidisciplinary approach, including therapeutic, pharmacological, and interventional approaches (2). Symptoms of CRPS may persist despite multiple conventional analgesic agents, resulting in significant health care expenditures and decreased quality of life (9).

Spinal cord stimulation (SCS) may offer effective pain relief in such cases. In rare refractory cases, an intrathecal drug delivery system (IDDS) may be indicated as an adjuvant to spinal neuromodulation (10). Prior literature has reviewed the utility of SCS and IDDS in pregnancy, but only in isolation (11-16). Here, we present a case of a patient that was established on SCS in combination with intrathecal ziconotide (ITZ) and baclofen (ITB) for pain management and continued these therapies throughout her pregnancy. No issues were reported during the prenatal and postnatal period.

Informed consent was obtained to present her case.

CASE PRESENTATION

A 24-year-old woman presented to the pain clinic with pain in her right knee and ankle as a sequela of a motor vehicle accident sustained 6 months ago. The patient had initially undergone open reduction and internal fixation of her right ankle following the accident but postoperatively continued to have severe pain. Upon presentation, the patient reported constant 10 out of 10 pain as measured on the Numeric Rating Scale that was sharp and cramping in quality with associated numbness and tingling paresthesia.

She reported minimal benefit with her current medication regimen, which included gabapentin 600 mg 3 times per day (TID), duloxetine 90 mg daily, acetaminophen 1,000 mg TID as needed (PRN), meloxicam 15 mg daily PRN, and lidocaine 5% topical patches (12 hours on and 12 hours off).

Prior relevant imaging, including computed tomography images, taken one month and 6 months postsurgery, revealed no issues with the hardware or healing of the ankle fractures (Fig. 1). Magnetic resonance imaging indicated diffuse osteopenia at the talus, tibia, and fibula. Prior electrodiagnostic testing was consistent with a right fibular nerve injury, which was re-demonstrated on repeat testing at a 6-month interval.

On physical examination, allodynia was noted in the right lower extremity, with fixed inversion of the right foot. The skin overlying the distal right leg and foot was purple and edematous. The patient met the subjective and objective criteria for CRPS type II with dystonia. At that visit's conclusion, gabapentin was switched to pregabalin 200 mg TID, and she was started on memantine as an off-label use for CRPS (5 mg up-titration every week to 20 mg daily), methocarbamol 500 mg TID PRN, and magnesium oxide 400 mg daily.

At 3 months after her initial presentation, she still reported severe pain as well as feelings of anxiety and depression. She was referred to a chronic pain psychologist for counseling who recommended acupuncture therapy, biofeedback, and desensitization therapies. Three months following that, she reported no significant improvement in her symptoms. At that time, she was then counseled for SCS therapy. She then underwent a successful trial and subsequent implant of a high frequency Nevro SCS with bilateral octopolar lead placement at the eighth and ninth thoracic vertebral bodies (Fig. 2). She then reported significant improvement of her pain and associated symptoms.

Six months following the SCS implant, the patient suffered a fall with a consequent worsening of her pain. Imaging revealed hardware loosening and a broken intraosseous nail, prompting hardware revision surgery. On follow-up to the authors' pain clinic, she reported significant pain in her right ankle; her right foot was inverted 30°.

Methocarbamol was substituted to baclofen 10 mg TID and up-titrated over the next 3 months to 20 mg TID. The patient reported mild improvement in cramping with baclofen titration, but still had significant ankle pain and paresthesias.

Given the refractory nature of her symptoms, a plan was made to trial ITZ. She underwent an intrathecal injection of 2.5 µg ziconotide and reported a greater than 30% improvement in her pain and associated symptoms. She subsequently underwent an implant of an intrathecal pump. A 20 mL Medtronic SynchroMed II™ (Medtronic, Inc.) was implanted into her left lower anterior abdomen which administered ziconotide at the rate of 0.5 µg/d (Fig. 2). Over the next few weeks, the ziconotide dose was escalated to 1.51 µg/d. Our patient reported notable symptom improvement, but she had continued cramping and dystonia. A plan was then made to add baclofen to the ITZ pump and taper off the oral baclofen and memantine. ITB therapy was initi-

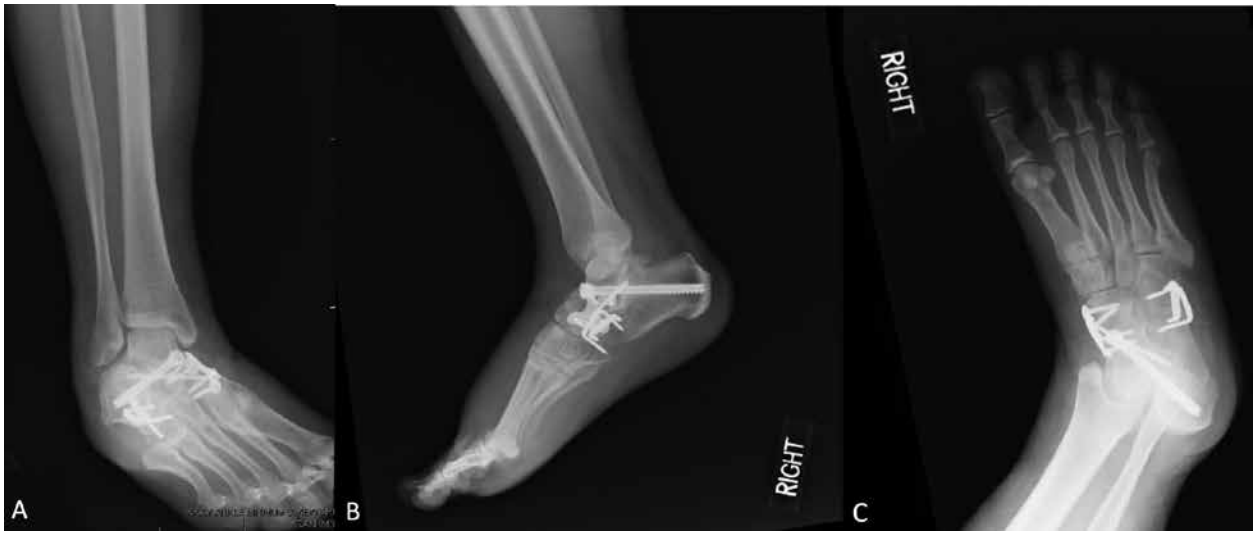

Fig. 1. Anteroposterior (AP) oblique internal rotation (A) and lateral (B) views of right ankle and AP oblique internal rotation (C) view of right foot demonstrating well-seated and intact surgical hardware without any other acute abnormalities.

ated at 25 µg/d and titrated up to 75 µg/d. She reported significant improvement in her overall symptoms with the combination of SCS and IDDS therapies.

Six months after initiating ITB therapy (2 years after her initial presentation), the patient became pregnant. She was advised to deactivate the SCS therapy due to unknown risks to the fetus and to taper off oral pregabalin. However, she reported increased pain immediately after discontinuing SCS therapy and decided to continue with SCS therapy. In consultation with an obstetrics specialist, and after being informed about the limited understanding of the effects of SCS therapy during pregnancy, a decision was made to continue both SCS and IDDS therapies.

Prenatal labs and first, second, and third-trimester fetal ultrasounds were within normal limits (Fig. 3). Subsequently, she gave birth to a healthy boy weighing 3,570 grams (7 pounds, 14 ounces) via normal vaginal delivery at 38 weeks and 6 days of gestation. The Apgar scores were 9 at both one and 5 minutes. The patient chose to breastfeed and remain off oral analgesic medications. At her one-year follow-up visit (approximately 4 years after her initial presentation), her child's progress was noted to be appropriate, achieving all developmental milestones. The patient continues to use SCS and IDDS therapies and has since resumed oral analgesic medications (she is currently taking pregabalin 50 mg twice daily along with 60 mg of duloxetine daily). She continues to have improvement in her pain, associated symptoms, and function.

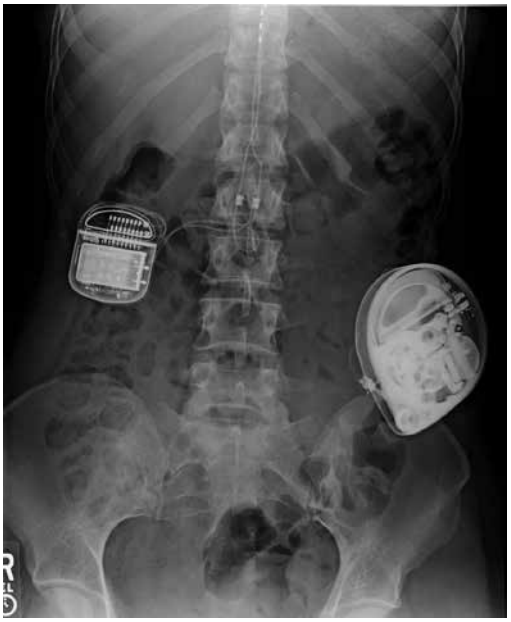

Fig. 2. Anteroposterior abdominal x-ray of the patient. The Nevro SCS System is located just above the right iliac crest with 2 octopolar leads at the T8-T9 interspace and the Medtronic intrathecal pump is in the left lower quadrant of the anterior abdomen.

DISCUSSION

Given women's predisposition to CRPS and the trend towards later maternity, the coexistence of CRPS and pregnancy seems likely to increase. Similar to other

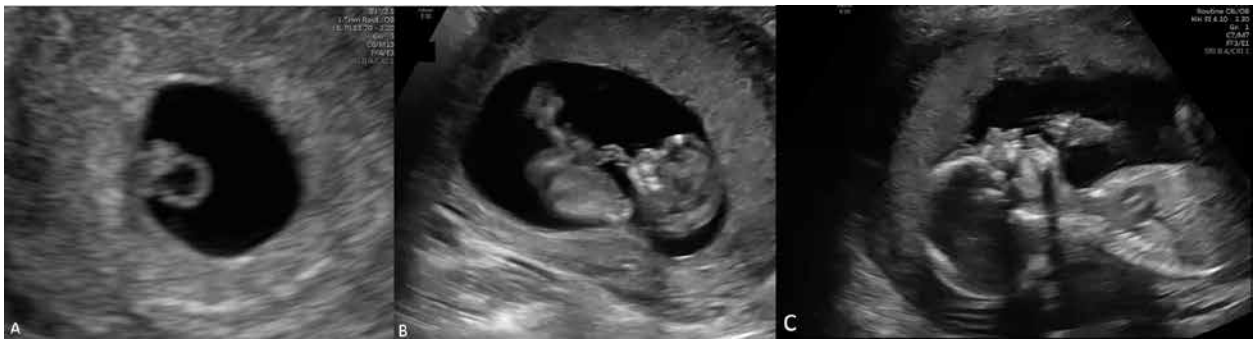

Fig. 3. Transabdominal ultrasound of fetus in 1st (A), 2nd (B), and 3rd (C) trimesters demonstrating normal fetal development.

chronic pain syndromes during pregnancy, safely and effectively treating CRPS in pregnancy presents a challenge for health care providers. Some have even postulated that safe medications for pain management during pregnancy and lactation do not exist (17). Thus, medical management requires careful consideration of known teratogenicity risk.

To assist with this, the US Food and Drug Administration previously created a classification to categorize the risk of teratogenic drugs during pregnancy. In this classification Category A was the safest category, but categories B, C, and D were also candidates for use in pregnancy depending on the clinical context (18,19). Most pharmacologic options for CRPS were labeled as category C, or those medications for which animal studies demonstrated a potential adverse effect without adequate studies in humans (6,18). However, as of June 2015, the US Food and Drug Administration eliminated this system as part of the Pregnancy and Lactation Labeling Rule in an effort to more clearly and more comprehensively clarify the risks and benefits of utilizing medications during pregnancy and lactation (20). A list of commonly utilized medications in CRPS and currently known safety profiles in both pregnancy and breastfeeding is provided in Table 1. Considering these risks, utilizing IDDS and SCS in women of child-bearing age with refractory CRPS warrants further exploration.

Intrathecal Baclofen (ITB)

Although not a first-line treatment for CRPS, ITB has demonstrated efficacy for treating dystonia related to CRPS (21,22). In isolation, ITB does not appear to provide substantial pain relief but may enhance the effects of SCS (23-26). Baclofen was previously classified as a category C medication, mainly due to studies on its oral use during pregnancy. Rat models evaluating high-dose oral baclofen demonstrated an increased risk of fetal omphaloceles; one case detailed human fetal baclofen withdrawal from a mother on high doses of oral baclofen (27). However, there are currently no known adverse neonatal outcomes following ITB use in pregnancy (14). ITB allows for therapeutic cerebrospinal fluid concentrations with plasma concentrations 100 times less than those associated with oral administration, typically between 0-5 ng/mL (28). These low levels of systemic absorption suggest that ITB may be safe for pregnancy (14). ITB may also be safe for breastfeeding, as a prior case report demonstrated marginal levels in breast milk from mothers on ITB (29).

Intrathecal Ziconotide (ITZ)

Ziconotide, a nonopioid medication, provides analgesia both when used in isolation and when used in combination with SCS (10,30-32). Ziconotide was also previously classified as a category C risk during pregnancy. Animal studies have demonstrated fetal toxicity at doses 700 times greater than the maximum recommended human daily dose of 19.2 μg/d (33). Prior evaluation of ITZ found that during 5 to 6 days of continuous intrathecal infusion (0.1-7.0 μg/h), less than 56% of patients had quantifiable plasma ziconotide levels (34). Most of the literature examining IDDS during pregnancy assesses ITB, but one case report details the successful use of ITZ for chronic headaches and arachnoiditis-associated pain over the course of multiple deliveries (15). ITZ is also suspected to be low risk during lactation due to its low systemic absorption, but there are currently no reports describing its use (35).

IDDS Safety Considerations

Given the paucity of literature, both ITB and ITZ require larger and well-controlled studies to analyze the

Table 1. Pregnancy and breastfeeding considerations for medications in CRPS.

Therapy	Efficacy in CRPS	Safety in Pregnancy (43)	Safety in Breastfeeding (35,44)
Vitamin C	Prophylactic use has reduced the onset of CRPS following trauma to upper or lower extremities (45)	Generally safe as long as below the RDA	Generally safe as long as below the RDA
Bisphosphonates	May reduce pain intensity and edema and improve ROM (2,46)	May be used if potential benefit outweighs risk, although pamidronate and zoledronic acid should be avoided given animal studies demonstrating fetal toxicity	Largely unknown if excreted in human breast milk and given risk of toxicity, extreme caution is advised
Corticosteroids	Short course appears to reduce pain in acute phase, but efficacy in chronic CRPS is unclear. Long-term use is not recommended (1,2)	May be used if potential benefit outweighs risk, although should avoid long-term use. Use during the 1st trimester may decrease human birth weight and increase risk of cleft lip. Have been shown to be teratogenic in animals	May be used if potential benefit outweighs risk. While transmitted in very small amounts in breast milk and poses theoretical risk, there are no known reported adverse effects to breastfed infants. If on high dose, consider waiting at least 4 hours after dosing
Free radical scavengers	Topical preparations of DMSO and NAC has reduced pain (4). Limited benefit in symptoms with mannitol (3,46)	DMSO has been associated with fetal toxicity in animals, while NAC and mannitol have not and may be used if potential benefit outweighs risk	Not yet known if excreted in breast milk and should only be utilized with caution
NSAIDs	Evidence does not support the use of NSAIDs in CRPS (1-3)	May be used if potential benefit outweighs risk until 20 weeks' gestation. Avoid use after 20 weeks due to risk of oligohydramnios, renal impairment, and premature closure of the ductus arteriosus	Generally safe (47)
Antidepressants (TCAs, SNRIs)	Effective in reducing neuropathic pain, but evidence is primarily anecdotal to support their use in CRPS (48)	May be used if potential benefit outweighs risk. No adverse effects to fetal development in animals at equivalent doses to humans, but associated with toxicity at doses greater than maximum human doses. There may be an increased risk to the fetus of using SNRIs late in 3rd trimester that may warrant tapering	May be used if potential benefit outweighs risk except for doxepin (risk of sedation and respiratory depression) and venlafaxine (RID of 7-8%) (6,49)
Gabapentin	May improve pain, but conflicting evidence on clinical significance of this relief (3,48,50)	May be used if potential benefit outweighs risk. There is evidence of fetal toxicity in animals at doses equivalent to those used in humans. Human observational studies do not suggest an increased risk of miscarriage or fetal malformation, but use late in pregnancy may predispose to pre-term labor, small for gestational age, and NICU admission (51,52)	Generally safe up to 2.1 mg/day (6)
SGB or LSB	Has previously reduced pain as well as increased ROM and participation in rehabilitation (1,2,6)	Lidocaine is thought to be safest and preferred with no evidence of animal embryo/fetal toxicity at doses 6.6 the maximum human dose	Generally safe
Ketamine	May improve pain and has induced remission in treatment-resistant patients, but literature is limited by low-quality evidence (2,53)	Should be avoided due to animal studies demonstrating significant neurotoxicity risk (54)	May be used if potential benefit outweighs risk but need to monitor for sedation, poor feeding, and poor weight gain. Consider avoiding breastfeeding for 6-12 hours after dosing

Table 1 continued. Pregnancy and breastfeeding considerations for medications in CRPS.

Therapy	Efficacy in CRPS	Safety in Pregnancy (43)	Safety in Breastfeeding (35,44)
Baclofen	Improves dystonic symptoms and has provided additive pain relief when used synergistically with SCS in refractory CRPS (21,22,26)	Oral baclofen has been associated with animal fetal toxicity and human fetal withdrawal, however there are no known adverse neonatal outcomes or withdrawal following the use of ITB (16,27)	May be used if potential benefit outweighs risk, particularly in IT dosing, due to its minimal excretion in breast milk. Need to monitor for sedation
Opioids	May reduce pain and improve function in short-term, but long-term use predisposes to risk of increased pain and dysfunction (48)	If potential benefit outweighs risk, oxycodone is preferred as it is the only opioid without evidence of fetal toxicity in animal studies (55)	Low-dose morphine is preferable to other opioids when necessary, although none are recommended and careful monitoring for infant drowsiness and CNS dysfunction is required (56)
Ziconotide	Has been used in isolation, combination IDDS therapy, and with SCS with improved pain, ambulation, and trophic changes (10,30)	May be used if potential benefit outweighs risk. No current evidence of fetal toxicity in animals until doses tremendously greater than maximum human dose	Unclear due to extremely limited data. Suspected minimal excretion in breast milk, although has not been quantified. If used, monitoring for sedation is required

CRPS = Complex regional pain syndrome; DMSO = Dimethylsulfoxide; IDDS = Intrathecal drug delivery system; IT = Intrathecal; LSB = Lumbar sympathetic blockade; NAC = N-acetylcysteine; NICU = Neonatal intensive care unit; NSAID = Nonsteroidal anti-inflammatory drug; RDA = Recommended dietary allowance; RID = Relative infant dosing; ROM = Range of motion; SCS = Spinal cord stimulator; SGB = Stellate ganglion blockade; SNRI = Serotonin and norepinephrine reuptake inhibitor; TCA = Tricyclic antidepressant

safety of these medications in pregnancy and breastfeeding before they can be routinely recommended. Physicians must counsel women of child-bearing age on potential risks/benefits prior to an intrathecal pump placement, including possible mechanical malfunction due to an expanding uterus altering the pump's position (16,36). Preconception assessment also includes evaluating how close the patient is to requiring pump replacement, as an early replacement before pregnancy may be indicated. The patient's obstetrician must be informed of existing IDDS therapies, especially as it pertains to considerations for cesarean deliveries (16).

Spinal Cord Stimulation (SCS)

SCS has demonstrated efficacy in reducing pain and improving quality of life in patients with CRPS refractory to conservative measures (1,37). Literature exploring its use in pregnancy is limited to observational studies, but 2 reviews state that it may be used cautiously (6,12).

In a review of 17 pregnancies involving SCS (for any indication), there were 10 full-term and 3 pre-term deliveries, but 2 mothers had a total of 4 miscarriages (6). Another study reviewed 13 cases of pregnancy in 8 women involving SCS (including some of the same cases from the first review), with 12 pregnancies resulting in the birth of healthy neonates – 10 of which were full-term (12). Both reviews included a case where a woman of unknown gestational age experienced a miscarriage 6 weeks after SCS implantation but noted the unclear contribution from her several category C oral medications (2,6,11). Across these reviews, SCS durations throughout pregnancy differed, with one patient turning SCS off as early as 8 weeks (6,38).

Given the observational nature of this research, it is impossible to determine the contribution that SCS may have had in the reported miscarriages. Therefore, pending future investigation, the decision to continue with SCS should remain individualized, following adequate preconception counseling on potential risks and benefits. Electrical current and electromagnetic field energy generated by SCS systems is one such possible concern. To date, animal studies suggest these are not detrimental to fetal development, but the effect on humans remains unknown (6,39). Literature describing SCS in lactation is extremely limited, but prior studies and our current case demonstrate no abnormalities with breastfeeding (12,38).

Similar to IDDS, the location SCS components should be evaluated as part of any preconception counseling and ideally before SCS placement in patients of child-bearing age. As much as possible, the implantable pulse generator, extension, and leads should be positioned away from the abdomen to reduce technical and biological issues during pregnancy as well as the labor and

delivery process itself (12). Additionally, the importance of a multidisciplinary approach that includes communication between obstetrics and pain management is necessary for optimizing the safety of the mother and fetus throughout the pregnancy.

Limitations and Future Directions

We present the first known case detailing the successful utilization of SCS and IDDS of both baclofen and ziconotide throughout pregnancy with healthy neonatal delivery. Before this, our patient experienced 2 spontaneous abortions. Occurring in 12% – 24% of clinically recognized pregnancies, spontaneous abortion is one of the most common adverse outcomes of pregnancy and may increase the risk of future miscarriages (40,41). However, there are also risks to discontinuing effective analgesia during pregnancy, including worsened pain and dysfunction, significant distress leading to the risk of self-neglect or inadequate prenatal care, and an elevated cortisol level (12,42).

Further research on the implications of SCS and IDDS on pregnancy and lactation is required to evaluate the risk and benefits of continuing these therapies. Ethical considerations will likely limit future research to observational studies. Normal developmental milestones in children at 2 and 4 years of age following pregnancies utilizing SCS have been reported (38). However, longitudinal observational studies examining the children and their mothers who utilized these therapies throughout pregnancy and breastfeeding may shed more light on the risk-benefit of continuing with these therapies during pregnancy and breastfeeding. Pending this research, the decision to continue these therapies must be considered individually, utilizing interprofessional teamwork. In addition, patients should be adequately counseled about the research gaps in this field.

CONCLUSION

CRPS represents a challenging chronic pain syndrome, especially when it manifests in women of child-bearing age. We present the first known case of a pregnant woman who continued SCS and IDDS throughout pregnancy and delivered a healthy baby boy who achieved appropriate developmental milestones at one year. Significant observational data are still required given the minimal literature on this topic and the special populations involved. Until then, the decision to continue these therapies should be considered on an individual basis and with close collaboration among the patient, obstetrics, and the pain management team.

Author Contributions

MG outlined the case report, conducted a comprehensive literature review, and drafted the manuscript. MG was also the submitting and corresponding author. AP, SS, and MF assisted with the editing of the case report. GC was responsible for identifying this case as a candidate for a case report, edited the manuscript, and guided the direction of the overall project. All authors contributed to the final approval of the manuscript.

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