Review Article

Complex regional pain syndrome and pregnancy

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ABSTRACT

Complex regional pain syndrome (CRPS) is a chronic pain condition predominantly affecting females of the reproductive age group. Association of CRPS and pregnancy has been increasingly reported in recent literature. Anesthesiologist and chronic pain physician may be involved in the management of CRPS during pregnancy and for peripartum anesthesia management for vaginal delivery or cesarean section. Any woman suffering from CRPS should be counseled about the limited therapeutic options available during pregnancy. Medical management of CRPS is complicated by risk to breast-fed babies and teratogenicity to fetus. However, interventional management in the form of transcutaneous electrical nerve stimulation and spinal cord stimulation may be used with due precautions. Multidisciplinary involvement of obstetrician, anesthesiologist, pain physician, and neonatologist is important to ensure successful outcome.

Key words: *Anesthesia, complex regional pain syndrome, pain, pregnancy*

INTRODUCTION

Complex regional pain syndrome (CRPS) remains a medical challenge due to its chronic nature, tendency to relapse, and disability over time. It occurs in middle-aged adults with a female preponderance of 2–4:1.[1] Pregnancy is a known predisposing factor of CRPS. But data are inadequate whether a pre-existing CRPS gets aggravated in a subsequent pregnancy.[2] Therefore, pre-existing CRPS should not be considered a contraindication for becoming pregnant.[2] As more number of working females wait till their late reproductive age to get pregnant, it may be increasingly common to encounter pregnant females with CRPS.

Due to wide heterogeneity in nomenclature, poorly understood pathophysiology, and lack of adequately powered randomized controlled trials (RCTs) on the management of CRPS, it is difficult to draw specific recommendations on this topic. Moreover, current evidence on the management of CRPS in pregnant women consists of case reports only. In the current review, we tried to summarize the available evidence on the diagnosis and management of CRPS, exclusively in pregnant women.

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DIAGNOSIS AND MANAGEMENT OF CRPS

To standardize the nomenclature and maintain uniformity, International Association for the Study of Pain (IASP) has adopted the term CRPS and suggested standard diagnostic criteria.[3] Diagnosis of CRPS requires the presence of regional pain and sensory changes following a noxious event. This may be associated with findings like abnormal skin color, temperature change, abnormal sudomotor activity, or edema. Two types of CRPS have been recognized: type I (also known as reflex sympathetic dystrophy) occurs without a definite nerve lesion and type 2 (known as causalgia) occurs with an identifiable nerve lesion. The combination of symptoms in CRPS may exceed what can be expected from the physical damage caused during and after the noxious event.[3]

Management of CRPS remains controversial. A variety of medications and techniques have been suggested in literature with limited evidence. These include physiotherapy, occupational therapy, pharmacological, psychological, regional anesthetic, neurolytic, and interventional neuromodulation techniques.

In a recent review by Tran *et al.*,[4] evidence of therapeutic options has been nicely summarized based on 41 RCTs. A

brief overview of the available options with their implications is presented in Table 1.

CRPS AND PREGNANCY

In this context, two aspects should be considered. Any female of reproductive age group who is suffering from CRPS may plan to bear a child or a pregnant woman can develop CRPS. Diagnostic criteria for CRPS remain the same in pregnancy. But various therapeutic options should be carefully considered before they are prescribed. Common medications used for CRPS may have teratogenic effects [Table 1] and implications for breast feeding[12] [Table 2], and the interventional techniques have their specific considerations in pregnant women, like effects on developing fetus, utero-placental circulation, or precipitation of labor.[13]

Woman suffering from CRPS wishes pregnancy

Any woman of reproductive age group suffering from CRPS should be made aware of the limited therapeutic options available during pregnancy. Teratogenic risk of medical therapy and sparse literature on interventional management leaves the therapeutic choice very limited. However, local anesthetic blockade, TENS, and SCS along with physiotherapy seem to offer some hope.

Pregnant woman develops CRPS

Pregnancy may be considered a predisposing factor for CRPS.[2] A pregnant woman can develop either new-onset CRPS or a relapse of CRPS. Onset of CRPS was found to be increased in the first 6 months following pregnancy.[14] Poncelet *et al*.[2] reported 9 cases and reviewed another 57 cases of reflex sympathetic dystrophy in pregnancy. Most often it involved the lower limbs, preferentially hip joint (88%), and 19% patients developed fractures. Exact pathophysiological mechanism remains unclear, but locoregional trophic disturbances due to mechanical changes in pregnancy have been attributed to the symptomatology.[2] Hypertriglyceridemia is considered a risk factor. Magnetic resonance imaging is the main diagnostic tool to detect the bony changes in pregnancy as X-ray and bone scintigraphy may not be safe. However, inadvertent exposure to technetium bone scan during the first trimester was not associated with increased birth defects.[15] General management involves non–weight-bearing rest, gentle physiotherapy, and non-opioid analgesics. These should be safe and unlikely to affect the course of pregnancy. Indication of cesarean section in parturients is purely obstetric and may be indicated in women with hip fracture. The efficacy of vitamin C in preventing CRPS after wrist fracture, foot or ankle surgery is well established. A daily dose of 500 mg for 50 days is recommended for this purpose.[5] Therefore, if a pregnant woman suffers trauma which can precipitate CRPS, prophylactic vitamin C may be

Table 1: Therapeutic options in complex regional pain syndrome

Therapy	Status in CRPS	Safety in pregnancy
Oral and intravenous bisphosphonates	Decrease pain and swelling, improve range of motion[4]	Category C
Calcitonin	Evidence does not support its use[4]	Category C
Free radical scavengers	Limited dose-dependent benefit with DMSO, short course of steroid[4]	Category C
Gabapentins	Marginal benefits[4]	Category C
Oral steroids (prednisolone, methylprednisolone)	4–12 weeks course in patients with or without cerebral infarct – significant improvement[4]	Category C
Ascorbic acid (vitamin C)	Prophylactic use can prevent CRPS after wrist fracture, foot and ankle surgery[5]	Category A
Epidural and intrathecal clonidine	Preliminary evidence shows effective alternative treatment – epidural clonidine 300 mcg for refractory lower limb CRPS[6]	Category C
Physiotherapy (PT) and occupational therapy (OT)	Benefit unclear, optimal type and frequency of PT and OT not yet determined[4]	May be used
Stellate ganglion blockade (SGB) and lumbar sympathetic blockade (LSB)	Local anesthetics in SGB reduce pain and increase the range of motion[7]	Lignocaine and phenol – no data Bupivacaine – category C
	Thermal radiofrequency ablation and phenol neurolysis of LSB provide equal analgesic benefit; the latter provides longer lasting sympatholysis[8]	Radiofrequency ablation for fibroids and cardiac arrhythmias has been safely used[10,11]
Transcutaneous electrical nerve stimulation (TENS)	More effective than placebo, easy to use[9]	Safe in pregnancy
Spinal cord stimulator	Significant pain relief for 2 years; beyond that, effect may be lost	May be used with caution
	Increased complications (as high as 72%) like pulse generator failure, lead displacement[4]	

DMSO, dimethyl sulfoxide; category C, studies on animals show adverse effect and toxicity on fetus. No adequate and well-controlled studies done on pregnant women. Drugs should be given only if the potential benefit outweighs the potential risk to the fetus

Table 2: Safety of drugs to breast-fed infants

Drug	Safety status
Gabapentins	Safe up to 2.1 g/day (monitor drowsiness and developmental milestones in infant)
Tricyclic antidepressants (TCA)	Generally safe (except doxepin)
Doxepin	To be avoided (sedative and respiratory depressant)
Topical local anesthetics	Safe
Oral bisphosphonates	Insufficient data
Steroids	Safe (oral prednisolone up to 50 mg/day and methylprednisolone up to 8 mg/day)
Clonidine	No data on epidural clonidine
	Oral clonidine – better to be avoided (high fetal serum level and possible negative effect on lactation)

considered. Lower limb CRPS following obstetric nerve palsy has been recently reported by Butchart *et al*.[16] A 28-year-old primigravida underwent instrumental delivery in lithotomy position under spinal anesthesia after prolonged labor and developed common peroneal nerve palsy in the immediate postpartum period. However, she continued to have edema, paresthesia, and allodynia of left foot, and developed CRPS in 2 weeks. This gradually resolved after medical management with gabapentin, ibuprofen, topical capsaicin, and physiotherapy after 6 months.[16]

MANAGEMENT

Medical management of pregnant CRPS patient is challenging as most of the drugs belong to category C or have some effect on breast-fed infants. Common medications found to be effective in CRPS are listed in Table 1, with their teratogenicity profile and effects on breast feeding given in Table 2. For acute pain control in CRPS patients, drugs like paracetamol (category B), nonsteroidal anti-inflammatory drugs (category C), and opioids (category C) are sometimes used. However, evidence of efficacy of these drugs originates from their use in neuropathic pain conditions.[17] Paracetamol may be safely used in lactating mothers, while during opioid therapy in the mother, the neonate should be monitored for drowsiness and adequacy of breast feeding.[16] Therefore, oral opioids and paracetamol should be considered safe in pregnancy (particularly beyond the first trimester), but reports of their use in pregnant CRPS patients are lacking.

There is paucity of data on the use of stellate ganglion blockade (SGB), chemical neurolysis, or lumbar sympathectomy in pregnant women. However, lumbar sympathetic block (LSB) has been used for labor analgesia during the first stage of labor in patients with history of back surgery or spine pathology.[18]

Similarly there are no data on radiofrequency ablation (RFA) for the treatment of CRPS in pregnancy. But the same has been used in pregnancy for other indications like ablation of intramural fibroid, aberrant cardiac conduction pathways, and twin reversed arterial perfusion (TRAP) sequence. RFA was found to be safe in these conditions, without any feto-maternal complications.[10,11]

TENS is a safe and easy-to-use technique in neuropathic pain conditions.[9] It has been safely used for labor analgesia[19] and in pregnant women with low back pain. In a prospective study, TENS was found to a safe and effective modality in pregnancy-related low back pain. Moreover, it provided significantly better pain relief than exercise and acetaminophen.[20] It may be considered a safe therapeutic option in pregnant women with CRPS.

Spinal cord stimulation (SCS) has been successfully used in pregnant women suffering from CRPS [Table 3].[21-24] It reduces pain and improves the quality of life, and thereby is an established treatment modality in CRPS.[25] In view of possible teratogenicity of drug therapy, SCS can be an alternative option in women with CRPS who wish to get pregnant. However, manufacturers do not recommend the use of SCS in pregnancy as its safety on developing embryo and fetus is not yet established. Factors to be considered in this context are: a) the effect of SCS on uterus and placenta, b) effect of SCS on the developing fetus, and c) use of SCS during labor and delivery.

Study to assess the effect of TENS on placental function in cases of placental insufficiency yielded an increase in human placental lactogen (HPL) and estriol concentration following TENS. If these results are extrapolated to SCS, the effects are not harmful for gestation.[21] SCS improves microcirculatory blood flow by antidromic action, and thereby it is effective in the treatment of angina pectoris and atherosclerosis obliterans. Similar effects may be produced on pelvic organs, but the effect of SCS on pelvic blood flow and conception has never been studied.[24]

Electromagnetic field (EMF) force generated by SCS may have some impact on conception and fetus. Increasing the exposure to maximum EMF (more than 1.6 μT) increases the risk of miscarriage and the relationship is more pronounced in early miscarriages (<10 weeks gestation). However, use of low-frequency EMF of 0.2 μT or electronically heated bed during pregnancy was not found to be associated with any risk of intrauterine fetal growth retardation or low birth weight infant.[26] Effect of SCS use during pregnancy on the offspring's development was further assessed by Bernerdini *et al*. in two such children of age 2 and 4 years, by using Denver's

Table 3: Case reports of pregnancy with spinal cord stimulator in CRPS

Study	SCS status	Pregnancy outcome
Segal *et al.* 1999[21]	Cervical SCS with gluteal pulse generator	Successful preterm vaginal delivery at 35 weeks
	SCS turned on during pregnancy	
Bernerdini 2010[22]	Low thoracic SCS with gluteal pulse generator	Successful full-term vaginal delivery
	SCS turned off before conception	Epidural analgesia used for labor
Bernerdini 2010[22]	Cervical SCS with gluteal pulse generator	Full-term cesarean section under general anesthesia
	First pregnancy – SCS turned off at 8 weeks for the rest of the pregnancy	Full-term cesarean section under epidural anesthesia
	Second pregnancy – SCS turned off at 5 weeks and again reactivated at 30 weeks due to pain	
Yoo *et al.* 2010[23]	Low thoracic SCS, pulse generator at anterior abdominal wall	Unplanned pregnancy accidentally detected during hospital visit for pain
	SCS was turned on during pregnancy	Early miscarriage 6 weeks after implantation of SCS
Ito *et al.* 2012[24]	Low thoracic SCS with gluteal pulse generator	Cesarean section under spinal anesthesia (term/preterm not mentioned)
	SCS turned on during pregnancy	

developmental scale. Both the children were reported to be developmentally normal. However, long-term effect is yet to be explored.[22]

Literature review revealed a total 17 pregnancies in 10 women with SCS *in situ* [Table 4].[24,27] Five patients had CRPS as the indication of SCS. In others, SCS was inserted due to failed back syndrome, low backache, or leg pain. Among the 10 patients, 2 had total four abortions after SCS was inserted. One patient had spontaneous abortion in the first trimester within 6 weeks of SCS. However, she was on eight different medications at that time and its role toward miscarriage has to be considered.[23] Another woman had one abortion before SCS placement and three other spontaneous abortions in the next 4 years after SCS placement before she had a successful pregnancy outcome at the age of 40. SCS was turned on during the entire pregnancy and she underwent cesarean section under spinal anesthesia.[24]

In most of the cases, pulse generator was placed in the gluteal region and the stimulating electrode in the cervical or thoracic spine. Pulse generator should be placed in the gluteal region as the abdominal placement can impair the function of SCS caused by enlarging abdomen during pregnancy. There is report of acute pain due to overstretching at the junction of epidural lead and lead extender, caused by enlarging abdomen during the second trimester of pregnancy in a patient who became pregnant 9 years after SCS placement.[28] The lead extender was surgically removed. Another patient had lead breakage after her third successful delivery, which was also attributed to pregnancy-related abdominal enlargement.[29] Stimulating electrode of SCS should preferably be placed in the cervical or high thoracic region to keep it away from the developing fetus. However, successful pregnancy outcome has been reported even when low thoracic SCS was placed and it was used throughout pregnancy. When SCS is being placed in women who wish to become pregnant, electrode lead should be accessed via high lumbar route keeping in mind that spinal or epidural route may be used in future for labor analgesia or anesthesia for cesarean section.[24]

Table 4: Pregnancy outcome in patients with SCS (all indications included)[21-24]

Outcome	Number of pregnancies (patients)
Total pregnancy (total patients)	17 (10)
Full-term delivery (total patients)	10 (6)*
Preterm delivery (total patients)	3 (3)
Miscarriage (total patients)	4 (2)

*One patient had two successful pregnancies: one full term and one preterm

Moreover, stimulation should be deactivated during vaginal delivery or cesarean section in order to prevent interference with the maternal electrocardiography monitoring and fetal heart rate monitoring, and bipolar electrocautery should be used.[27] No difficulty in lactation or breastfeeding subsequent to SCS was mentioned.[27] Both milk ejection and milk flow were reported to be normal.[22]

CONCLUSION

With the tendency of late maternity, coexistence of CRPS and pregnancy may be on the rise. Diagnostic criteria of CRPS are no different for pregnant women. Drug therapy may be complicated by the risk of teratogenicity to the fetus, and information on interventional management of CRPS in pregnancy is sparse. However, based on available literature, we suggest that any female of reproductive age group suffering from CRPS should be made aware of the limited management options available during pregnancy and pregnancy test should be carried out in them before prescribing any medication with known teratogenicity. If the women wish pregnancy, interventional management like TENS or SCS

may be considered. However, the patient should be counseled about the pros and cons of the SCS, and the same should be implanted and used with all due precautions throughout the pregnancy and peripartum period. In the event pregnancy is accidentally detected in patient already on treatment, drug therapy should be immediately reviewed, teratogenic drugs should be discontinued, and alternate therapies should be considered.

Finally, successful pregnancy outcome as well as proper CRPS management will depend on multidisciplinary involvement of anesthesia, obstetrics, neonatology, and pain medicine, and this should begin early in pregnancy.

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