Pathophysiological and hormonal changes affecting pain during pregnancy: a review

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Abstract
Introduction
There are significant pathophysiological and hormonal changes that take place during pregnancy, which affect almost every system in the body and contribute to successfully overcoming the challenges of pregnancy and labour. The changes noted in the first trimester of pregnancy are mainly of hormonal aetiology, considering the fact that the secretion of progesterone, oestrogens, human chorionic gonadotrophin, prostaglandins and endorphins is significantly increased. The aim of this review is to discuss the pathophysiological and hormonal changes affecting pain during pregnancy.

Conclusion
Pain during pregnancy can become a serious condition, which negatively influences the woman’s quality of life.

Introduction
On review of literature, it appears that with the progression of pregnancy some hormonal changes could potentially lead to symptoms varying from discomfort to pain that requires treatment, despite the fact that the threshold for pain is increased due to the reduced enzymatic degradation of endogenous opioids, such as endorphins and encephalin. We discuss the most common conditions of pain that present in the course of gestation in the following sections.

Literature review
We searched for relevant publications in the Pubmed database. The keywords used included the terms: pregnancy, pain, musculoskeletal, back pain, headache, migraine, anaemia, TENS, syndrome, sciatica, preterm labour, analgesics and transfusion. In addition, we reviewed the references of the initially retrieved articles to identify additional relevant publications. We focused on articles describing the categories, the risks, the causes, the mechanisms as well as the treatment of pain in pregnancy. We identified 383 articles as well as the computerised search. The information found in 14 articles of this search was used to form our narrative review.

Discussion
Pain derived from the musculoskeletal, nervous and circulatory system
All pregnant women essentially report symptoms from the musculoskeletal system; however, only 25% experience symptoms that have a significant impact on daily life. In 80% of all pregnant women, there is an interstitial oedema that predisposes to compression and entrapment of nerves over the last 8 weeks in gestation. The basic changes that contribute to the discomfort or true pain in pregnancy are the relaxation of ligaments, the increase in the body weight of the pregnant and the increase in the size of the uterus. In pregnancy, there is a relaxation of ligaments that is considered a normal change and is due to the production of hormones such as relaxin, which is produced by the corpus luteum, and oestrogens. Relaxin exerts an effect on the morphology of the connective tissue fibres in the pelvis by reducing their diameter, which results in their degradation. There is a correlation between the mean value of relaxin plasma levels and the pain located at the joints and lower back pain in gestation. The peak levels of relaxin are noted at the 12th week of gestation, and subsequently there is a gradual decrease till the 17th week. The increase in relaxin levels reaches up to 50% the peak value. The increase in body weight during gestation is normal. However, in combination with the relaxation of ligaments this may lead to joint pain. An increase in weight by 20% may increase the pressure applied to the joints by 100%. The increase in the size of the uterus may lead to hyperlordosis, pressure and forward flexion of the pelvis, against which the sacroiliac joints resist. With the progression of gestation, the above-mentioned events are aggravated due to relaxation of the sacroiliac ligaments. These changes through a mechanical way lead to an increase in the pressure that is applied in the lower back, the sacroiliac joints and the pelvis.

Back pain
Back pain occurs in approximately 50% of the pregnant women and is considered to be the most common musculoskeletal symptom during pregnancy. Wang et al.² classified back pain as upper back pain (pain at the level of the thoracic spine), middle back pain (pain at the level of the lumbar spine) and lower back pain.
pain (pain located at the sacroiliac region that deteriorates with progression of pregnancy). Risk factors are the history of previous back pain, the extremes of age for the pregnant woman, the low socio-economic level, the multiparity, spondylolisthesis and the excessive increase in body weight over pregnancy. Nevertheless, some authors believe that back pain is not related to the increase in body weight of the mother or foetus during gestation. The causes of back pain are either hormonal or mechanical. The hormonal effects take place from the first trimester of pregnancy and involve the relaxation of the pelvic ligaments by relaxin. These results in a linear effect on the stability of the pelvis by the plasma mean levels of relaxin. Relaxation of the pelvic ligaments results in dysfunction of the sacroiliac joints thus leading to low back pain. There is a direct correlation between the plasma levels of relaxin and the percentage of pregnant women with lower back pain. The mechanical causes involve the increase in the size of the uterus, which leads to a forward flexion of the sacrum. They also involve the increase in the lumbar curvature of the spine and the aggravation of the lumbar lordosis, which leads to a stenosis and the aggravation of the lumbar in the lumbar curvature of the spine crum. They also involve the increase in body weight during pregnancy. Mechanical causes of back pain of pregnancy. The diagnosis should include good medical history, comprehensive physical examination, radiography imaging (if necessary, with a dose <10 rads; a greater dose may lead to foetal growth restriction and mental retardation), magnetic tomography and electromyogram. Treatment involves advice and consultation to the pregnant for the most common causes of back pain, restriction of activities and regular resting periods, exercises for strengthening the dorsal and abdominal muscles, exercises in the water, physiotherapy, cold or warm dressings, lateral bedside position and support of the abdomen with a wedge-like pillow, transcutaneous electrical nerve stimulation (TENS—which has not been extensively studied in pregnant women but is considered rather safe), pelvic support bandage, acupuncture (in cases of lower back pain in the second and third trimester, where an improvement of approximately 72% was noted), administration of acetaminophen (which is considered the treatment of choice, whereas anti-prostaglandins are contraindicated because they are implicated in early closure of the foetal arteries), administration of cyclobenzaprine, oxycodone and prednisolone, and the oral administration of opioids for small time periods. There is no literature evidence on the safety and efficacy of the epidural administration of steroids. Surgical management of the intervertebral disc is recommended for pregnant women, who are rendered incapable of performing activities. Their pain does not regress even in the supine position and moreover, the patients display progressive neurological complications.

Symphysis pubis pain during pregnancy

The symphysis pubis is normally dilated but not more than 1 mm at 10–12 weeks of gestation under the effect of relaxin. Pain at the symphysis pubis may be due to relaxation of the pelvic ligaments (occurs in 1 in 36 pregnant women), inflammation and osteitis of the area and fracture, which is rare and is caused by the rupture of the ligaments that support the symphysis pubis. This may happen in precipitate vaginal delivery that can lead to widening of the symphysis pubis to more than 1 cm (ref. 1), or in sudden and excessive abduction of the thighs during delivery. The most characteristic symptom of a fracture is the sudden acute pain at the symphysis pubis area that radiates to the back and to the thighs. Diagnosis is confirmed from the significant sound that can be heard, through palpation and from the acute pain. The pain at the symphysis pubis is mild and continuous or may develop into acute pain that radiates to the thighs and low down to the back. Pain from this area regresses gradually a few days or weeks after delivery. Treatment during gestation is conservative and includes self-control of movements by the gravid patient, simple resting or occasional bed-rest. It is wise to administer anti-inflammatory agents after delivery, such as intraligamentous injections of lidocaine and steroids to shorten the duration of the symptoms. Treatment of the fracture is conservative and involves lateral position bed-rest with flexed knees and pelvic support with

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a belt or bandage, walking-support when symptoms allow. Surgical intervention is recommended when the space between the pubic bones is >4 cm.

Scoliosis
Severe scoliosis that is related to pregnancy is rare and occurs with an incidence of 0.03%. Pregnancy can aggravate severe scoliosis and cause a significant degree of back pain and cardio-respiratory complications.

Pain from entrapment of peripheral nerves and neuropathies
Pain from nerve entrapment and neuropathies are rare in pregnancy and have an incidence of 1%. Peripheral nerves are susceptible and their injury and damage may be caused by several different mechanisms, such as pressure, ischaemia, tension and destruction. Pressure and tension are the most common mechanisms. Pressure is directly proportional to the oedema of pregnancy. Nerve damage due to pressure most often involves the median nerve of the carpal tunnel and the perineal nerve at the level of the head of the fibula. Nerve damage due to tension develops when the tension applied on a nerve exceeds the elasticity level of the nerve and also of the connective tissue surrounding it. The combined application of pressure and tension on a peripheral nerve may cause ischaemic damage. Peripheral nerve damage usually recovers completely after delivery.

Carpal tunnel syndrome
The incidence of carpal tunnel syndrome in pregnancy is 2%-25%. The aetiology includes increased levels of prolactin and oedema of the pregnant woman that compresses the median nerve during its course within the carpal tunnel. It presents with pain, paraesthesia and numbness of the first three fingers often bilaterally and occurs in the third trimester of pregnancy. Pain is aggravated at night or with repeated movements of flexion and extension. Treatment is conservative and includes warm dressings, injection of steroids in cases of severe symptoms and neutral positioning of the wrist with use of a splint.

Lateral femoral cutaneous nerve paraesthesia (meralgia paresthetica syndrome)
The pressure applied to the nerve due to lumbar lordosis is considered as the possible cause of this syndrome. The femoral cutaneous nerve is a pure sensory nerve and innervates the antero-lateral surface of the thigh. Its damage is manifested by a sense of burning, pain or numbness at the respective area. This syndrome regresses after delivery.

Upper limb pain
The increase in the interstitial fluid and the increase in the plasma levels of hormones are implicated for the probable inflammation, tenosynovitis of the first dorsal compartment of the wrist (De Quervain’s syndrome). It manifests with local sensitivity. Treatment is conservative with restriction in activities and movements of the hand. In persistent cases, it is recommended that a local infiltration of the sheath and/or tendon with corticosteroids be performed. The change in the posture of the pregnant woman due to the displacement of her centre of mass because of the size and weight of the uterus is implicated for the compression of the ulnar and median nerve, which manifests with numbness of the fingers.

Lower limb and hip joint pain
Its aetiology involves back pain that radiates to the lower limbs, disease of the hip joint, relaxation of the ligaments of the lower limb joints, hip joint osteoporosis and femoral head necrosis. The vast majority of disorders concern the femoral head of the hip joint and the knee meniscus.

The osteoporosis and osteonecrosis in pregnant women is a result of the pressure on the femoral head of the hip joint because of the progressive increase in body weight and usually occurs at the third trimester of gestation. Prompt diagnosis and treatment with body weight modification prevents any long-term implications. Calcitonin and bisphosphonates are administered for treatment. There is a debate regarding the use of bisphosphonates that they may possibly adversely affect the development of foetal bones and that they affect the foetal Ca²⁺ levels. Prognosis is good as all symptoms regress after delivery, as long as they were entirely due to gestation and they did not pre-exist.

Haemorrhoids
They quite often cause symptoms in pregnant women ranging from discomfort to pain. The most common cause is constipation. Progesterone also causes relaxation in the walls of the veins and the large intestine. Finally, the increase in the size of the uterus compresses the haemorrhoid plexus preventing the abduction of blood. Management is conservative.

Lower limb cramps
For a number of years, it was considered that the main cause was the limited absorption of Ca²⁺, or the disorder in the calcium-phosphorus balance. Another theory is that the increase in the size of the uterus prevents the blood circulation in the pelvic vessels and also applies pressure on the pelvic nerves. Treatment is conservative and includes exercises that improve the blood circulation, regular elevation of lower limbs and administration of calcium and phosphorus.

Lower limb varices
Varices are caused owing to the pressure by the gravid uterus on the pelvic veins when standing upright and on the inferior vena cava in supine position. Moreover, the increase in
the levels of progesterone leads to relaxation of the walls of the veins and their valves. Varicose veins result in a sense of discomfort to the lower limbs. Treatment is conservative and includes the use of elastic stockings, avoiding long time periods of standing, regular elevation of lower limbs, bedrest in lateral position, mild exercises and moderate walking.

**Migraine–headache during pregnancy**

It is considered to be one of the most common neurological symptoms during pregnancy. The most common types of headache in pregnancy are tension headache, migraine and headache that is related to gestational hypertension.

**Tension headache**

It is caused by the contraction of muscles and is the most common type of headache during pregnancy. Symptoms involve vague continuous pain over the entire head. Deterioration is gradual and symptoms remain for a long time period. Although the causes are unknown, it is related to anxiety and stress. The treatment includes acetaminophen, aspirin, opioids, tricyclic antidepressants and benzodiazepines. Benzodiazepines should be avoided during the first trimester of pregnancy. Mild opioids and tricyclic antidepressants are considered safe and effective and do not affect the development of the foetal nervous system.

Others believe that migraine is due to a primary vascular disorder or is due to a disorder in the nor-adrenergic nervous system. Migraine occurs in 13%–17% of young-aged women and rarely in elderly women. The effect of hormones in headache or migraine is known. The drop in oestrogen levels is related to deterioration in symptoms. Treatment involves the administration of ergotamine in combination with caffeine. The ergot family of alkaloids is contraindicated in pregnancy as they are related with the induction of precipitate labour and probable teratogenicity. Promethazine relieves the symptoms of nausea and vomiting. β-Blockers (propranolol) are used on a preventative basis only in severe symptoms as they cross the placenta. Also, calcium-channel antagonists have been occasionally used. The administration of triptans in pregnant women, which represent a new selective serotonin antagonist, has not been sufficiently evaluated and is assumed that when administered in high doses they may increase the frequency of genetic anomalies, as it has been shown in animal studies. There are contradictory data that refer to the relation between migraine and pre-eclampsia. Recent studies show that women with a history of migraine have a higher risk of demonstrating pre-eclampsia. Cerebral ischaemia has been reported after the use of terbutaline in women with migraine. For this reason, it should be avoided in women with a history of vascular aetiology headache.

**Migraine**

It rarely presents for the first time in pregnancy and usually pre-exists. Migraine is typically one-sided and is sometimes accompanied by nausea and vomiting. Its duration varies from a few hours to days. Migraine can be preceded by skotomas (visual disorders) and focal neurological symptoms. Some researchers claim that the cause of migraine is a neurogenic vasospasm that is followed by vasodilation of the cerebral vessels.

It is a hereditary, multisystem disease. Patients with sickle cell disease are either homozygotes with haemoglobin (Hb) SS or heterozygotes with Hb SA. Hb S occurs due to the replacement of the amino acid valine by glutamic acid in the 6th amino acid position of the β-chain in the Hb molecule. The most serious cause of sickling of the red blood cells is hypoxia, which occurs when PO$_2$ < 50 mm Hg and is completed when PO$_2$ is approximately 23 mm Hg. Other causes are percentage of Hb S > 50% of total Hb, dehydration that leads to increased viscosity of the blood, hypotension that results in vascular stasis, hypothermia, acidosis and shivering. The incidence of pneumonia and pyelonephritis is increased among pregnant women with sickle cell disease in comparison to pregnant women without sickle cell disease. Sickling of the red cells leads to obstruction of the vessels mainly in the chest, abdomen, spine, long bones, limbs and brain. It manifests with episodes that vary in severity and duration usually between 3 and 5 days and correspond to the areas of obstruction of the vessels and occur at approximately 50% of pregnant women. Pregnancy aggravates the complications of sickle cell anaemia. Maternal mortality is 1% and the main cause is pulmonary embolism. Foetal mortality is 20% and is due to the increased incidence of preterm delivery, placental abruption and pre-eclampsia. Sickle-cell anaemia is a chronic disease and is treated depending on the severity of symptoms. Management involves aggressive hydration for the reduction of blood viscosity, O$_2$ administration, exercise, temperature maintenance, TENS application, administration of analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs, mild opioids given orally or administration of morphine in the form of PCA (Pain Controlled Analgesia) in severe cases of patients who have been admitted, and finally the placement of an epidural catheter, administration of local anaesthetics and opioids that act twofold. They decrease the blood viscosity through hydration and vascular dilatation, and they induce analgesia through the administered opioids. When specific indications arise (aplastic anaemia and pregnancy), it may be appropriate to transfuse blood units. The targets of blood
transfusion is a level of haemoglobin >8 g/dL and to ensure that haemoglobin A is >40% of the total Hb. The reduced Hb levels of approximately 10 g/dL during gestation reduces the frequency of painful episodes but does not appear to modify the maternal and foetal mortality. Bone marrow transplantation is another experimental treatment that appears to be well promising for the future.

**Conclusion**

Pain during pregnancy can become a serious condition, which negatively influences the woman’s quality of life. The pathophysiological and hormonal changes affecting this pathological entity have been reviewed.

**Abbreviations list**

Hb, haemoglobin; TENS, transcutaneous electrical nerve stimulation.

**References**


