Headache and pregnancy

Cefaleia e gravidez

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ABSTRACT

Headache in pregnancy is a peculiarity of woman life phase. Correct diagnosis in pregnancy is the best thing for a management gold standard. Some secondary headaches that mimic migraine may begin during pregnancy, and can be caused by vasculitis, brain tumor, pituitary tumor, arteriovenous malformation, sinus disease, idiopathic intracranial hypertension, subarachnoid hemorrhage, stroke, cerebral venous thrombosis, pre-eclampsia and eclampsia. These headaches must be correctly diagnosed. At the conclusion, if a pregnant patient presents primary headache, it will be necessary to treat her. The classic teratogenic risk occurs from the 29th day to the 70th day of gestation. Women with severe headache during this period should be treated because nausea and vomiting in association with pain can be teratogenic to the fetus. Non-pharmacological techniques are effective for acute and preventive treatment and should be applied. If drugs are necessary, will be choose minimal doses and medications that causes fewer problems in pregnancy. Management of pregnant women with migraine should be done with caution, keeping in mind the low level of scientific evidences.

Key words: Pregnancy; Headache; Migraine; Treatment.

RESUMO

Cefaleia na gestação é uma peculiaridade de uma fase da vida da mulher. O diagnóstico correto da cefaleia na gravidez é a chave para um tratamento de excelência. Algumas cefaleias secundárias que mimetizam migrânea podem se iniciar durante a gestação, e podem ser causadas por vasculites, tumor cerebral, tumor hipofisário, malformação arteriovenosa, sinusopatias, hipertensão intracraniana idiopática, hemorragia subaracnóidea, acidente vascular encefálico, trombose venosa cerebral, pré-eclâmpsia e eclâmpsia. Tais cefaleias devem ser diagnosticadas corretamente. Ao se concluir que a paciente grávida apresenta cefaleia primária, é necessário tratá-la. O risco teratogênico clássico das drogas ocorre a partir do 29º até o 70º dia a partir do 1º dia da última menstruação da mulher. Mulheres com cefaleia intensa nesse período devem ser tratadas, pois náuseas e vômitos em associação com dor podem ser teratogênicos ao feto. Técnicas não farmacólogicas são efetivas para tratamento agudo e preventivo e devem ser empregadas. Se drogas forem necessárias, escolher as menores doses e que causem menos problemas na gravidez. O tratamento da gestante com enxaqueca deve ser realizado com muita cautela, tendo-se em mente que o nível de evidência é baixo.

Palavras-chave: Cefaleia; Gravidez; Enxaqueca; Tratamento

INTRODUCTION

Pregnancy is a peculiar woman life phase, considered optional. It usually occurs during woman´s professional highest peak. Headache in pregnancy is a woman's particularity, and like other disturbances in this phase, must be seen with caution. Its progress must be followed and its treatment must be carefully addressed.[1]

Correct diagnosis

The diagnosis of a headache disorder must be correct for a suitable management. In pregnant and lactating woman this is done through the Classification of the International Headache Society (2004).[2]

On the anamnesis of a pregnant woman with headache, it´s important to always ask her if she had headaches before pregnancy, or if the headaches started during pregnancy, or if she had a prior headache and there were changes in the headache characteristics during the pregnancy.

It is always necessary to distinguish between pre-existing headaches and those initiated during pregnancy because there may be three possibilities: (1) monitoring the behavior of an existing headache prior to pregnancy, during pregnancy; (2) appearance of a new headache during pregnancy; and (3) the woman had presented a headache before getting pregnant and then develops a new one during pregnancy.

SECONDARY HEADACHES

Migraine-like headache that began during pregnancy may be secondary to vasculitis, brain tumor, chorio-carcinoma, pituitary tumor, arteriovenous malformation (AVM), sinus disease, idiopathic intracranial hypertension, subarachnoid hemorrhage, stroke, cerebral venous thrombosis, pre-eclampsia and eclampsia.[3,4]

Some comments about specific secondary headaches:

1. The diagnosis of sinusitis is often overstated, chronic sinus does not cause headache;[3,4]

2. Only 48% of brain tumor patients develop headache during pregnancy. Pregnancy does not increase the risk of brain tumor;

3. Pregnant women have 13 times the risk of having a stroke. One of the most common stroke during pregnancy is cerebral venous thrombosis. Most cases present neurological deficits, but the superior sagittal sinus thrombosis may present with progressive headache, without neurological signs or symptoms;

4. Subarachnoid hemorrhage explains 50% of intracranial bleeding during pregnancy. Subarachnoid hemorrhage may mimic eclampsia. Most cases of intracranial hemorrhage, especially in the eclampsia group, result from hypertension. Illicit substances (alcohol and cocaine) is a cause of subarachnoid and intracerebral hemorrhage during pregnancy;[3]

5. Differential diagnosis of thunderclap headaches of sudden onset includes reversible cerebral vaso-constriction syndrome, subarachnoid hemorrhage by aneurysm, cerebral venous thrombosis, dissection of the carotid or vertebral artery, intraparenchymal hemorrhage and pituitary apoplexy. Neuroimaging is required in such cases. Reversible cerebral vasoconstriction syndrome encompasses a diverse group of conditions, including hypertensive encephalopathy and vasculopathy associated with pregnancy and the postpartum period (postpartum angiopathy). Reversible cerebral vaso-constriction syndrome is characterized by sudden onset of a severe headache that subsides within a few days to weeks and resolves in most patients, approximately 12 weeks after the presentation. A similar syndrome can be seen with pre-eclampsia and eclampsia occurring before birth or postpartum. A diagnosis of reversible cerebral vaso-constriction syndrome requires the exclusion of other causes of headache accompanied by tomography or magnetic resonance imaging and magnetic angiography resonance to evaluate arterial and venous vasoconstriction or cerebral edema, and exclude cerebral venous thrombosis. Cerebrospinal fluid obtained via lumbar puncture can eliminate vasculitis or infection.[5]

Symptomatic headaches require neuroimaging or lumbar puncture to diagnose. The guidelines for neuro-imaging in patients who are or may be pregnant are:

1. Determinate the necessity and the potential risks of the procedure.

2. If possible, perform the examination during the first 10 days postmenses, or if the patient is pregnant, delay the examination until the third trimester or preferably postpartum.

3. Pick the procedure with the highest accuracy balanced by the lowest radiation.

4. Use MRI if possible.

5. Avoid direct exposure to the abdomen and pelvis;

6. Avoid contrast agents.

7. Do not avoid radiologic testing purely for the sake of the pregnancy.

8. If significant exposure in incurred by a pregnant patient, consult a radiation biologist.

9. Consent forms are neither required nor recommended.[4]

Head CT is relatively safe during pregnancy and is the study of choice for head trauma and possible non-traumatic subarachnoid, subdural or intraparenchymal haemorrhage.

MRI is preferable for all other non-traumatic or non-haemorrhagic craniospinal pathologies. The potential risks of MRI in pregnancy are still controversial. First use angiography to evaluate suspected vascular pathology, but, when necessary, angiography is reasonably safe in pregnant patient.[4]

A CT scan exposes the mother to a radiation of <0.01 Gray (Gy), while the threshold of fetal damage with ionizing radiation directly into the maternal pelvis is >0.1 to 0.2 Gy. To maintain the safety margin, the National Council for Radiation Protection and Measurements grouped the acceptable limits of radiation in all scan sat 0.05 Gy. MRI does not show the same level of risk associated with ionizing radiation.

Gadolinium-based contrast agents have been associated with the development of nephrogenic systemic sclerosis . This condition is rare and has been reported to occur in patients with compromised renal function. Gadolinium can cross the placenta into the fetal circulation and, subsequently, is excreted into the amniotic fluid, where the agent can remain for an extended period of time. No prospective studies with large numbers of patients have evaluated the risk of teratogenic or mutagenic effects.

The American College of Radiology Guidelines Document for Safe MR Practices recommends that pregnant patient should only receive gadolinium-contrast agents after careful consideration of the risk-benefit ratio. Iodinated CT contrast agent has been associated with contrast-induced nephropathy in as many as 21% of patients who had a baseline glomerular filtration rate of <50 ml/min/1.73 m^2. Nephropathy induced by iodinated CT contrast agent is usually reversible, but the condition can be associated with nonrenal complications that can prolong hospital stays and increase in-hospital mortality. Free iodide in the contrast medium given to the mother has the potential to depress fetal and neo natal thyroid function. Neonatal thyroid function should, therefore, be checked after delivery in such patients. The risk associated with absorption of contrast medium during lactation is small and can be considered insufficient to warrant stopping of breastfeeding. The neonatal thyroid should be checked after labor in such patients.[5-10]

Potential indications for computed tomography or MRI in headache investigation during pregnancy are the same as an average patient with suspected secondary headache (Table 1).

Table 1 - When suspect of a secondary headache

First episode of sudden onset of headache, or worst headache of life
Followed by disturbance of consciousness, fever, neck stiffness
Changes in frequency, intensity, or the clinical characteristics of headache attacks
Abnormal neurological examination (followed by signs/irritative or deficitary neurological symptom)
Progressive headache or new daily persistent
Neurological symptoms that do not fulfill the criteria for migraine with typical aura
Persistent neurological deficit
Evidence of a defined focal lesion in the electroencephalogram (EEG)
Changes in skin or orbit suggestive of AVM
Comorbidity of partial seizures
Followed by endocrine disorders or high blood pressure;
Related to coughing or physical effort
Triggered by sexual activity, and vomiting lasting hours
Changing pattern; new headache superimposed on the old one
Start after 50 years of age

MEDICATIONS ON PREGNANCY AND FETUS

If the conclusion is that the pregnant patient presents primary headache, it will be necessary to treat headaches during pregnancy. Then, there will be a concern with regarding the treatment.

Management

Treatment of pregnant women is a part of medicine based in low scientific quality of evidence. The experience in treating these women comes from case-control studies and and populational retrospectives.

Tables with drugs risks in pregnancy risk of learning disabilities are deficient, and 40% of the drugs do not have a listed category. The decision about what to use during pregnancy should be made case by case, using incomplete information.

It must always be applied in migraineurs pregnant women non-pharmacological treatment which is free from risk to fetus and mother.[1,11]

The classic teratogenic risk occurs from the 29th day to the 70th day of gestation (after the first day of the woman's last menstruation). Women with severe headache during this period should be treated because nausea and vomiting resulting due to pain may be teratogenic to the fetus.[12]

The evaluation of the first trimester is therefore a serious methodological error, only the second and third months represent the critical period of most major congenital abnormalities (CAs). On the other hand, we know that the critical period of some CAs exceeds the end of third month, e.g., the critical period of posterior cleft palate and hypospadias covers the 12th-14th and 14th-16th weeks of gestation, while the critical period of undescended testis and patent *ductus arteriosus* is 7 to 9 months and 9 to 10 months, respectively. Thus, the optimal approach is to consider the specific critical period of each CA separately.[12]

The FDA (Food and Drug Administration) lists five categories of labeling for drug use in pregnancy. These categories provide therapeutic guidance, weighting the risks as well as the benefits of the drug. An alternate rating system is TERIS (an automated teratogen information resource wherein ratings for each drug or agent are based on a consensus of expert opinion and

the literature) which was designed to measure the teratogenic risk to the fetus from drug exposure (Tables 2 and, 3).

Table 4 presents some drugs and their risk categories (FDA and TERIS)[3-5,12-16]

Table 2 - FDA drugs risk categories, and the corresponding TERIS at the first column

Category A (TERIS - none None-minimal)	Controlled humans studies show no risk
Category B (TERIS - Minimal)	No evidence of risk in humans, but there are no controlled humans studies
Category C (TERIS - Undetermined)	Risk in humans has not been ruled out
Category D (TERIS - Minimal-small)	Positive evidence of risk to humans from human and/or animal studies
Category X (TERIS - High)	Contraindicated in pregnancy

Table 3 - Teratogenic information service (TERIS) risk rating

Risk proportion	Definition
N	None (A)
N-Min	None-minimal (A)
Min	Minimal (B)
Min-S	Minimal-small (D)
S	Small
S-Mod	Small-Moderate
Mod	Moderate
H	High (X)
U	Undetermined (C)

Preventive or prophylactic treatment

Classes of drugs that can be used like prophylactic on pregnant woman migraine:

Beta-blockers

– Propranolol – adverse events: delay uterine growth, hypoglycemia, bradycardia and breathless;

– Atenolol – adverse events: lower weight at birth;

– Metoprolol -adverse effects: growth delay;

– Labetalol[11]

Corticosteroids – helpful for occasional use in a regimen of short prophylaxis helps in the maturation of fetal lungs.[15]

Prednisone and prednisolone – no risk, they must have preference over dexamethasone, as the latter crosses the placental barrier.

Serotonin reuptake inhibitors (SSRIs) – fluoxetine and sertraline are useful in migraine and comorbid conditions such as anxiety or depression.

Magnesium, riboflavin, pyridoxine hydrochloride – there is no evidence of risk of multiple congenital anomalies associated with periconceptional use of vitamin supplementation.[17]

Symptomatic treatment of migraineur pregnant women

Measures that can be used taken symptomatic therapy in migraine of pregnant women are:

– Hydration.

– NSAIDs (ibuprofen, naproxen, can close the fetal *ductus arteriosus*), corticosteroids (useful, occasional).

– Aspirin (low dose).

– Common analgesics (acetaminophen).

– Narcotic analgesics.

– Chlorpromazine, promethazine, metoclopramide;

– Triptans (naratriptan and sumatriptan) (no evidence of abnormality, can be used if other drugs do not solve, to avoid during the 2nd and 3rd months).

– Pyridoxine (for nausea – not teratogenic).

What not to use in pregnant women with headache

Natural or herbal therapy (because they are less studied); feverfew (by presenting possible teratogenicity); ergotamine, dihydroergotamine (are contraindicated for showing an association with increased risk of neural tube defects and a higher proportion of premature births, neonatal lower weight birth and low gestational age;[18] benzodiazepines and barbiturates (for cleft palate occurrence and heart and urogenital defects), valproate and divalproex[1] (for neural tube defects such as bifid spina and myelomeningocele, cardiac abnormalities, such as levocardia, aortic stenosis, patent *ductus arteriosus*, tetralogy of Fallot, partial right bundle branch block, ventricular septal defect, and various facial defects); Receptor inhibitors of the angiotensin converting enzyme (ACE) (association with fetal kidney problems).[1]

CONCLUSIONS

It is recommend that women at childbearing age take vitamin supplement with 0.4 g of folic acid to reduce risk of neural tube defect. If pregnancy is desired by the migraineurs, discontinuation of medications must be made before conception. If the woman becomes pregnant during treatment, the conduct will depend of the used medication.

Non-pharmacological techniques are effective for acute and preventive treatment.

Table 4 - Risk factors for some drugs (FDA e TERIS)

Analgesic	FDA	TERIS
Aspirin	C (D - if 3rd trimester)	Minimal
Acetaminophen	B	None
Caffeine	B	None
Dipyrone	C	
AINH		
Ibuprofen	B (D - if 3rd trimester)	Minimal
Indomethacin	B (D)	None
Naproxen	B (D - if 3rd trimester)	Undetermined
Narcotics		
Butorphanol	C (D)	
Codeine	C (D - prolonged or term pregnancy)	Unlikely
Meperidine	B (D - prolonged or term pregnancy)	None-minimal
Methadone	B (D)	None-minimal
Morphine	B (D - prolonged or term pregnancy)	None-minimal
5HT Antagonists		
Pizotifen	Does not apply (C)	Security no stablished
Methisergide	X	Security no stablished
Methylergonovine	C	Undetermined
Serotonergic agonists and ergot		
Ergotamine	X	Undetermined/ Minimal
Ergotamine	X	Undetermined/ Minimal
Sumatriptan	C	Undetermined
Corticosteroids		
Dexamethasone	C	None-minimal
Prednisone	B	None-minimal
Prednisolone	C (D- if 3rd trimester)	None-minimal
Barbiturates		
Butalbital	C (D)	None-minimal
Phenobarbital	D	None-minimal
Benzodiazepines		
Chlordiazepoxide	D	None-minimal
Diazepam	D	None-minimal
Clonazepan	C	Undetermined
Antihistamines		
Cyclizine	B	Undetermined
Cyproheptadine	B	Undetermined
Dimenhydrinate (dramamine)	B	None-minimal
Meclizine	B	None-minimal
Oxcarbazepina	D	
Ethosuximida	C	
Neuroleptics		
Phenothiazines		
Chlorpromazine	C	None-minimal
Prochlorperazine	C	None
Butyrophenones		
Haloperidol	C	None-minimal

Table 4 - Risk factors for some drugs (FDA e TERIS) (Cont.)

Analgesic	FDA	TERIS
Antiemetics		
Metoclopramide	B	Minimal
Dimenhydrinate	B/D	
Ondansetron	B	
Domperidone	C	Undetermined
Others		
Emetrol	B	
Doxylamina		None
Pyridoxine	B	None
Lithium	D	
Beta-blockers	Dosage	
Atenolol	50-120 mg/d D	Undetermined
Propranolol	40-320 mg/d C (D- prolonged or term pregnancy)	Undetermined
Nadolol	40-240 mg/d C (D- prolonged or term pregnancy)	Undetermined
Metoprolol	50-100 mg/d C (D- prolonged or term pregnancy)	Undetermined
Timolol	C (D - prolonged or term pregnancy)	Undetermined
Antidepressives		
Tricyclics		
Amitriptyline	10-250 mg/d C	Unlikely
Nortriptyline	10-100 mg/d C	Undetermined
Imipramine	C	Unlikely
IRSS		
Fluoxetine	10-80 mg/d B	None
Paroxetine	10-50 mg/d C	Undetermined
Sertraline	B	Unknown
Calcium Channel Blockers		
Verapamil	240-720 mg/d C	Undetermined
Diltiazem	120-360 mg/d C	Undetermined
Flunarizine	5-10 mg/d (Does not apply (C)	Segurity no established
Anticonvulsants		
Valproic acid	D	Moderate
Divalproex	500-3000 mg/d (D)	Moderate
Topiramate	D	
Carbamazepine	B	
Gabapentin	C	Undetermined
Lamotrigine	C	Undetermined
Phenytoin	D	
Oxcarbazepina	D	
Ethosuximida	C	

If drugs are necessary, you will choose small doses and drugs that cause fewer problems in pregnancy.

Experts (Hungarian, American and European) after several reviews, ask if we can improve our uncertain ties about the treatment of the pregnant migraineurs and answer that little can be expected about changing the situation in the future. Forbidding to use drugs during pregnancy is mostly due to ignorance of its action over the fetus than the opposite.

The treatment of pregnant women with migraine should be done with caution, bearing in mind that the evidence is low, and this fact will not change in the future. Headache in pregnancy is a vast theme and should be studied in a more complex way because it involves two beings: the pregnant woman and the fetus. The message here is that there is still much to be done in order to clarify this so great universe of headache in pregnant women.

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