PREGNANCY AND GASTROINTESTINAL MEDICATION IN AMBULATORY PRACTICE

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Abstract

Gastrointestinal pathology is relatively frequent in the pregnant woman. In the case of the pregnant woman, the doctor may be faced with some chronic diseases prior to pregnancy, as well as acute or chronic diseases occurring during pregnancy. The prescription of medication in pregnancy is a real challenge to the doctor, who must always evaluate the risk/benefit ratio. The paper reviews the therapeutic peculiarities of the most common gastro-intestinal disorders in pregnant women.

Keywords: pregnancy, gastrointestinal medication, fetal risk.

SARCINA ŞI MEDICAŢIA GASTROINTESTINALĂ ÎN PRACTICA MEDICULUI DIN AMBULATOR

Rezumat

Patologia gastrointestinală este relativ frecvent întâlnită la femeia însărcinată. La femeia gravidă, medicul se poate confrunta atât cu unele afecţiuni cronice preexistente sarcinii, cât şi cu boli acute sau cronice survenite în cursul sarcinii. Prescrierea medicaţiei în sarcină reprezintă o adevărată provocare pentru medicul practician, iar în luarea unei decizii terapeutice acesta va trebui întotdeauna să evalueze raportul risc-beneficiu.

Lucrarea de faţă realizează o trecere în revistă a particularităţilor terapeutice din principalele afecţiuni gastrointestinale întâlnite la femeia gravidă.

Cuvinte cheie: sarcină, medicaţia gastro-intestinală, risc fetal.

Introduction

Given the absence of prospective controlled clinical trials in pregnancy, data on the safe administration of gastrointestinal medication to pregnant women are limited, so that absolute safety cannot be ensured for any drug. The risks generated by the existing pathological condition should always be balanced with the data on the safety of the chosen medication [1].

It is generally admitted that tests performed on animals do not ensure the safe administration of the preparation to pregnant women, nevertheless providing some important indications regarding the adverse effects on the product of conception [2].

Before starting a treatment it is important to consider all information we have about the safety of the chosen drug.

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Classification of drugs regarding to their safety during pregnancy

For a better evaluation of the risk/benefit ratio in prescribing medication for pregnant women, FDA (Food and Drug Administration) has developed a classification of drugs in 5 risk categories:

FDA (Food and Drug Administration) categories regarding the safety of medication in pregnancy (adapted from [1,2])

Category A: controlled studies in pregnant women have not demonstrated, for any trimester of pregnancy, any risk for the fetus;

Category B: studies performed in animals have evidenced no risk for the fetus, but there are no controlled studies performed in pregnant women;

Category C: studies performed in animals have demonstrated adverse effects on the fetus, while there are no controlled studies in pregnant women;

or

there are no studies in animals and no controlled

studies in pregnant women. These drugs can only be used in cases in which the potential benefit justifies the taking of a potential risk for the fetus.

Category D: controlled studies performed in pregnant women have demonstrated the presence of a risk for the fetus.

In certain exceptional cases, these drugs can be used (e.g. if the drug is required in a disease that threatens the pregnant woman's life, and safer drugs are not available or are not effective).

Category X: controlled studies performed in animals or pregnant women have demonstrated fetal malformations or a risk for the product of conception, and the risk of the use of the drug by the pregnant woman is obviously higher than any potential benefit. The drug is clearly contraindicated in pregnant women or women who wish to get pregnant.

In the pregnant woman, the doctor can be faced with some chronic gastrointestinal diseases prior to pregnancy (inflammatory bowel disease, irritable bowel syndrome, etc.), as well as with acute or chronic diseases occurring during the course of pregnancy.

Most frequent gastrointestinal diseases during pregnancy in ambulatory practice

Nausea and vomiting of pregnancy

This is the most common medical condition of pregnancy [3], affecting 40-90% of pregnant women [2], with a higher incidence in the first trimester of pregnancy.

Vitamin B6 (pyridoxine) administered in doses of 10-25 mg 3 times a day is considered to improve these symptoms [5,6] and is included in category A, according to FDA [2].

Metoclopramide is frequently used in the treatment of pregnancy disease and seems to be safe (category B) [1,2,6,7]. The doses used are 10 mg every 8 hours.

Emetiral (prochlorperazine), included in category C, is widely used in USA [8] in doses of 5-10 mg 3 times a day.

Romergan (promethazine), also included in category C, is also widely used, the recommended doses being 12.5-25, 4 times a day [8].

Ondansetron is included in category B, being considered as a low risk drug, and can be recommended in pregnancy [1,2,6,8]. The doses used are 8 mg 2-3 times a day.

Gastroesophageal reflux disease (GERD) and ulcer disease (UD)

The symptoms of GERD are frequently present in pregnancy (40-80%). UD is less frequently found in pregnancy, and complications are less common [8]. The *non-pharmacological measures* usually recommended in GERD (change in diet, life style) do not ensure, most of the times, the desired results, given the pressure exerted by the pregnant uterus.

Antacids based on calcium, magnesium and aluminium used in therapeutic doses are considered to be safe in pregnancy [1,6,9]. They represent the first intention medication in GERD and UD in pregnant women.

Antacids based on sodium bicarbonate will be avoided, because these can accelerate metabolic acidosis in the mother and the fetus.

Sucralfate (category B) is considered to be safe, including in the first trimester of pregnancy [1,8].

H2 receptor blockers will only be considered in cases not responding to antacids. The largest number of data are available on cimetidine; information obtained from prospective studies supports its safety in pregnancy [4]. There is also good experience with ranitidine in this sense. In contrast, for famotidine and nizatidine, the currently available data are fewer, which is why cimetidine and ranitidine are preferred [1].

Of the *proton pump inhibitors* (PPI), omeprazole has proved its toxicity for the embryo and the fetus [1,2], which is why pantoprazole, esomeprazole and lansoprazole are preferred, being considered to be safe [10]. A large cohort study undertaken in Denmark to assess the association between exposure to PPI during the first trimester of pregnancy and the risk of major birth defects found no significantly increased risk of major birth defects corelated to PPI intake [11].

Bismuth subsalicylate, included by FDA in class C, is not recommended in pregnancy, being considered teratogenic [8,2].

Eradication of Helicobacter pylori (HP) and pregnancy

Though the exposure to HP appears to be associated with an increased risk of hyperemesis gravidarum [12], the treatment of HP infection according to the known schemes (association of two antibiotics and one PPI) is generally not recommended during pregnancy, because the symptomatology of ulcer disease responds to antisecretory medication, and the short term complications of HP infection are very few; in contrast, the antibiotics included in the treatment schemes have a teratogenic potential [4].

Constipation

Constipation is frequently reported in pregnant women. Pregnancy may influence the appearance of constipation or may aggravate pre-existing constipation. The first recommended measures will certainly be aimed at an adequate diet and life style. Studies reveal the fact that women are more frequently prescribed laxatives during pregnancy, compared to the period preceding it [13].

Volume laxatives: wheat fibers prepared as powder, synthetic methyl cellulose derivatives, grains obtained from the seeds of plants (psyllium) are considered safe and effective [8].

Hyperosmolar laxatives based on polyethylene

glycol and non-absorbable polysaccharides (lactulosis, sorbitol) can also be used in pregnancy.

Emollient laxatives can be recommended, if needed, only for a short duration in pregnancy, because they favor vitamin malabsorption [14].

Stimulating laxatives : bisacodyl seems to be safe in pregnancy [15], being included in class B, according to FDA.

Acute diarrhea

The most common etiological factors of acute diarrhea are viruses, bacteria (and their toxins) or parasites.

In the majority of the cases, the infectious episode is self-limited, so that support therapy is sufficient; this involves water-electrolyte re-equilibration and adequate diet.

Symptomatic medication:

Imodium (loperamide) should be avoided during the first trimester of pregnancy because it increases the risk of fetal cardiac malformations [1,2,16,17]. In later pregnancy it is included in risk category B and can be recommended.

Cholestyramine (category C) may cause the malabsorption of liposoluble vitamins, when used in high doses over long time periods.

Diosmectite (Smecta) is not absorbed, therefore it can be recommended in pregnancy.

If *antibiotherapy* is required, the benefit/risk ratio will be taken into consideration. Ampicillin, as well as the amoxicillin/clavulanic acid combination, are included in category B and can be safely administered to pregnant women. Also, azithromycin (category B) does not seem to be associated with congenital defects.

Albendazole, although teratogenic in animals (category C), has been the object of studies suggesting the fact that its use in the eradication of parasitoses in pregnant women is beneficial for the evolution of pregnancy [1].

Data referring to the use of furazolidone and tinidazole in pregnancy, although limited, do not suggest an increase in the incidence of congenital abnormalities.

Metronidazole (included in category B), although apparently associated with a slight increase in the risk of palatal defects, is considered to have a low risk in pregnancy when used in the short term [1]; however, the majority of clinicians limit its use to the second and third trimesters of pregnancy [9].

Quinolones are associated with the appearance of joint and cartilage defects in the fetus, which is why they belong to category C.

Doxycycline, tetracycline and *biseptol* are known as teratogenic and are contraindicated in pregnancy.

Irritable bowel syndrome (IBS)

The treatment of *constipation* and *diarrhea* in IBS is subject to the recommendations presented in the sections on chronic constipation and acute diarrhea.

There are limited data regarding the safe administration of *antispastic medication* to pregnant women. *Mebeverine (duspatalin, colospasmin)* is not teratogenic in animals and no adverse effects on the fetus have been reported, but information in this respect is scarce. Consequently, it should be used with caution and in low doses, for short time periods. The case of *otilonium bromide (spasmomen)* is similar.

Tricyclic antidepressants are not recommended during pregnancy; *amitriptyline* and *nortriptyline* (both included in category D) have been incriminated in the appearance of limb malformations.

Selective serotonin reuptake inhibitors (*fluoxetine, paroxetine*) included in category C are not recommended in pregnancy, because in the first trimester they increase the risk of spontaneous abortion, and their administration during the last trimester is correlated with the appearance of neurological and behavioral disorders in the newborn [2,8].

Inflammatory bowel disease (IBD)

Studies performed in pregnant women with Crohn disease or ulcer colitis have evidenced the fact that the evolution of pregnancy depends on the activity of the disease; the presence of an active IBD during the course of pregnancy increases the risk of complications, including premature birth and fetal hypotrophy. IBD activity during pregnancy seems to correlate with that at the time of conception, which is why women with IBD are recommended to become pregnant at a time when the disease is not active [8].

Aminosalicylates represent the basic medication for IBD during pregnancy. *Sulfasalazine, mesalazine* and *5-aminosalicylic acid* can be used under safety conditions, being included in category B. Sulfasalazine requires folic acid supplementation (2 mg/day) for the prevention of neural tube defects, its antifolic effect being known. *Olsalazine* is the only category C representative of the class.

Corticosteroids can be administered in pregnancy, being included in risk category B, except for budesonide which, in the absence of controlled studies on pregnant women, belongs to class C [2,8].

When *antibiotherapy* is required in IBD, its duration is usually several weeks, so that metronidazole and quinolones will only be administered to carefully selected cases, with a categorical indication and for an as short as possible time period [1].

Methotrexate is included in category X, because it has a teratogenic and pro-abortive effect, which is why it is strongly contraindicated in pregnancy [1,2,17,9].

Azathioprine and *6-mercaptopurine* have proved to be teratogenic in animals, while data available in humans are contradictory, which is why FDA included these drugs in category D [2].

Biological agents, *infliximab* and *adalimumab* (category B), are considered to have a low risk in pregnancy and can be indicated for the maintenance of IBD remission, the benefits obtained being superior to any known risk.

Conclusions

The prescription of medication in pregnancy is a real challenge to the doctor. Before any drug is recommended to a pregnant woman, the obstetrician should be consulted and the pregnant woman should be informed of the safety, benefits and risks involved.

With very few exceptions, all chemical substances can cross the placenta and in relation to their liposolubility and chemical structure, they reach variable concentrations at embryonic or fetal level. It is obvious that the teratogenic effects of drugs depend on the dose, but also on the chronological factor, i.e. the stage of development of the product of conception [2,5].

As a basic rule, the minimum dose allowing the expected effect will always be administered, and the duration of treatment should be as short as possible; it is recommended to avoid molecules recently introduced in the therapeutic armamentarium, because these have not yet passed the test of time [5]. For chronic diseases, drug therapy will be delayed, if possible, until after delivery.

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