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Teratogenic Mechanisms Associated with Prenatal Medication Exposure

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Abstract – Birth defects may originate through multiple mechanisms and may be caused by a variety of possible exposures, including medications in early pregnancy. In this review, we describe six principal teratogenic mechanisms suspected to be associated with medication use: folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption, and specific receptor- or enzyme-mediated teratogenesis. Knowledge about these mechanisms, for some of which evidence is mainly derived from animal models, may not only be relevant for etiologic and post-marketing research, but may also have implications for prescribing behavior for women of reproductive age. Since combinations of seemingly unrelated medications may have effects through similar teratogenic mechanisms, the risk of birth defects may be strongly increased in multi-therapy.

Mots clés :
anomalies congénitales ;
composants pharmaceutiques ;
grossesse ;
tératologie

Résumé – Mécanismes tératogéniques associés à l'exposition médicamenteuse prénatale. Les malformations congénitales peuvent provenir de multiples mécanismes et peuvent être causées par des expositions variées, incluant l'exposition aux médicaments en début de grossesse. Dans cette revue, nous décrivons six principaux mécanismes d'effets tératogènes suspectés d'être associés à l'utilisation des médicaments : antagonisme des folates, déficit des cellules de la crête neurale, perturbation endocrinienne, stress oxydatif, étiologie vasculaire, et tératogénèse médiée par une enzyme ou un récepteur spécifique. La connaissance de ces mécanismes, dont certains éléments de preuve proviennent principalement des modèles animaux, pourrait non seulement être pertinente pour la recherche étiologique et post-commercialisation, mais également avoir des implications sur les comportements de prescription aux femmes en âge de procréer. Dans la mesure où des médicaments, apparemment différents, peuvent avoir des effets malformatifs résultant de mécanismes identiques, le risque de malformations congénitales peut être fortement augmenté en cas de polythérapie.

Abbreviations: see end of article.

1. Introduction

Prescription medication use is common in developed countries, with prevalence estimates ranging between 27 and 99%, depending on the data sources used and the types of medication included.[1] Although classical examples of human teratogens include some medications, such as thalidomide and isotretinoin, the human teratogenic risk is undetermined for more than 90% of drug treatments approved for marketing in the United States since 1980.[2] Several reasons for this lack of knowledge can be identified, including problems in extrapolating results from animal studies to human pregnancy and the exclusion of pregnant women from premarketing clinical trials. However, medication use is sometimes unavoidable in the treatment of pregnant women, for instance among women diagnosed with severe depression or hypertension, epilepsy, or diabetes.

Major birth defects, generally defined as structural malformations that are of medical, surgical, or cosmetic importance, occur in approximately 2% of births.[3] Birth defects are a heterogeneous collection of various disorders with each specific defect having its own distribution in the population and its own risk factors.[4] In 2008, 376 000 children under the age of 5 years died of congenital abnormalities worldwide, ranking birth defects among the main causes of infant mortality in developed countries.[5] A particular birth defect may be caused by a wide range of factors, including genetics, environmental agents, medications, and physical conditions, and by different underlying mechanisms. A specific pathogenic process may lead to

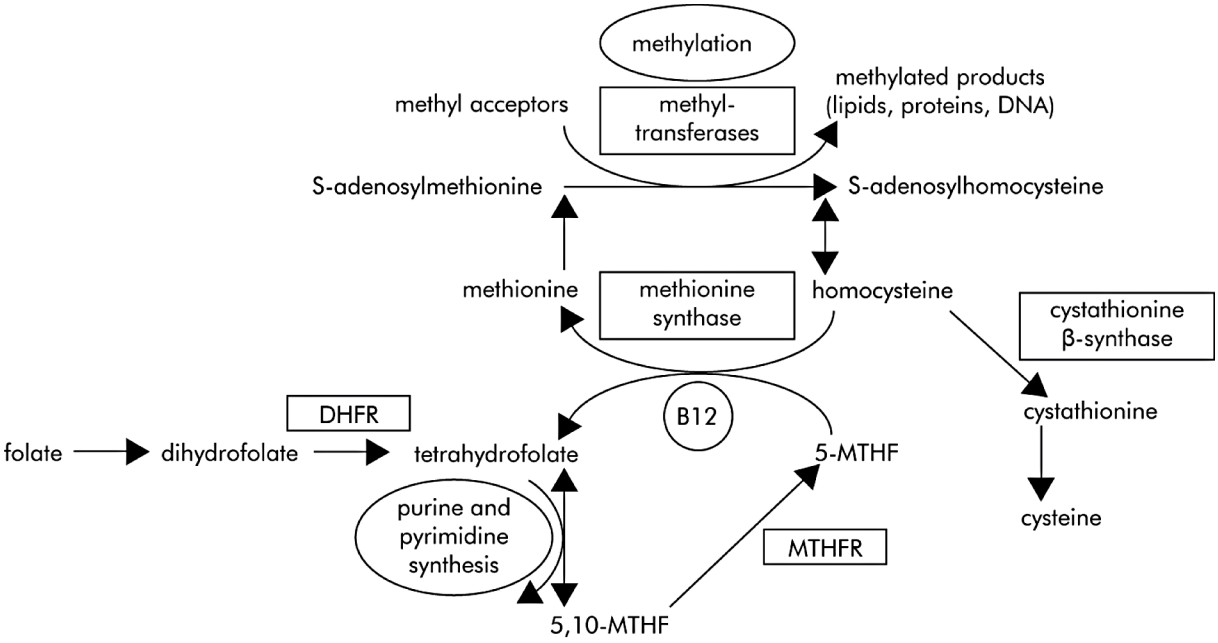

Fig. 1. Folate-homocysteine-methionine metabolism. Adapted from van Gelder *et al.*[8] by permission of Oxford University Press.
B12: vitamin B_{12}; **DHFR**: dihydrofolate reductase; **MTHF**: methyltetrahydrofolate; **MTHFR**: methylenetetrahydrofolate reductase.

different outcomes for chemical exposures depending upon such factors as embryonic age at exposure, duration and dose of exposure, and genetic susceptibility.[6,7] Although the mechanisms by which medication may be involved in the etiology of birth defects are still not completely understood, we summarized the six most important teratogenic mechanisms known today in this review.

2. Teratogenic mechanisms of medical drugs

2.1. Folate antagonism

Folate-dependent processes are essential for fetal growth and development as 5-methyltetrahydrofolate, the main form of folate in the blood circulation, acts as an essential co-enzyme in many biochemical reactions by being an acceptor or donor of one-carbon units in, for example, purine and pyrimidine synthesis and deoxyribonucleic acid (DNA) methylation reactions (figure 1).[8] Furthermore, DNA methylation is known to be involved in the epigenetic control of gene expression during development. Therefore, medications that disturb the folate metabolism may have teratogenic effects through inhibition of the folate methylation cycle. Folate antagonists can be classified into two general groups of drugs. The first group consists of competitive inhibitors of dihydrofolate reductase (DHFR) and includes methotrexate, sulfasalazine, triamterene, and trimethoprim, which block the conversion of folate to tetrahydrofolate by binding irreversibly to the enzyme.[9] The second group of drugs may antagonize other enzymes in the folate metabolism, impair folate absorption, or increase folate degradation. This group primarily consists of anti-epileptic drugs, including valproic acid, carbamazepine, and phenytoin.

The teratogenicity of folate antagonists was first suggested by reports of women who were given aminopterin in the first trimester of pregnancy to induce abortion.[10] Some anti-epileptic drugs (*e.g.*, carbamazepine and valproic acid) are generally known to increase the risk of folate-sensitive birth defects, including neural tube defects (NTDs), orofacial clefts, and limb defects. Four epidemiologic studies determined the effect of folate antagonists as a group on the occurrence of birth defects, generally showing increased risks, but with inconsistent results for DHFR inhibitors.[11–14] The fact that folic acid supplementation in the periconceptional period decreases the risk of NTDs[15] implies a causative role of folate deficiency in the etiology of these defects. Indeed, low blood folate status has been associated with an increased risk of NTDs.[16,17] In addition, a low maternal vitamin B_{12} (cyanocobalamin) status has been shown to be an independent risk factor for NTDs.[18,19] Vitamin B_{12} is a cofactor to methionine synthase, which converts homocysteine into methionine (figure 1). Therefore, a shortage of this vitamin also leads to a distorted folate metabolism.

The exact mechanism by which disturbances of the folate metabolism increase the risk of NTDs has not been unraveled yet. Women pregnant with a fetus with an NTD have significantly higher plasma and amniotic fluid homocysteine levels than control subjects,[20,21] which may result from folate deficiency. Several hypotheses have been