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Higher intake of medications for digestive disorders in children prenatally exposed to drugs with atropinic properties

Digestive medications in children prenatally exposed to atropinic drugs

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Abstract

Background. Childhood digestive disorders are common and sometimes unexplained. Some drug exposure during the embryofetal digestive system development may contribute to increase childhood digestive disorder, especially drugs acting on the cholinergic system, widely present on the digestive tract.

Purpose. To assess the use of medications for digestive disorders in childhood (0 – 3 years) associated with prenatal exposure to drugs with atropinic properties.

Methods. Children from POMME (*PrescriptiOn Médicaments Mères Enfants*), a database of reimbursed drugs to children during their prenatal life and childhood, were included (N=8,372). Each drug prescribed during antenatal life was assigned an atropinic score (0=null, 1=low, 3=strong) according to its capacity to exhibit anticholinergic effects. Atropinic burden *in utero* consisted in the sum of the atropinic scores of drugs prescribed. The association between the use of medications for digestive disorders and atropinic drug exposure was estimated by a Poisson regression.

Results. More than 30% (N=2,652) of the children were prenatally exposed to atropinic drugs. They had significantly more periods of digestive disorder drug use (5.0 *versus* 4.0) than unexposed children (RRa = 1,11 [1,06 ; 1,16]). The strength of the association increased with both the atropinic burden and the number of atropinic drug dispensations.

Conclusions. Our results suggest an association between fetal exposure to atropinic drugs and a higher number of digestive drug prescriptions in childhood. Thus, drugs with atropinic properties are potentially inappropriate medications for the pregnant women and their children.

Key Points

- The French cohort POMME holds information on drug prescriptions and reimbursements for the children from the first day of their intrauterine life until they reach 6 years of age.
- More than 30% of the children were prenatally exposed to atropinic drugs.
- These exposed children have used significantly more drugs for digestive disorders, especially if their atropinic burden in utero was high. Some digestive disorders in early childhood could be partly the consequence of a prenatal exposure to atropinic drugs.

1. INTRODUCTION

Childhood digestive disorders are common and cause of concerns because they affect the quality of life of the children and their families. They represent a significant reason for outpatient health care use (1,2). The main known causes of childhood gastrointestinal disorders are infections, inflammatory bowel diseases, genetic susceptibilities and psychological and socio-environmental factors(3). In most cases, the combination of several of these factors is responsible for childhood digestive disorders. However, other mechanisms remain likely unexplained.

Some authors have already suggested that *in utero* drug exposure may affect digestive functions of the child. Nijenhuis *et al.* reported that children exposed *in utero* to selective serotonin re-uptake inhibitors and tricyclic antidepressants were more likely to receive laxatives between 0 and 5 years (4). This could be explained by an effect of antidepressants on the development of the enteric nervous system. There are probably other drugs that can disturb the embryonic or fetal digestive system development resulting in gastrointestinal disorders in childhood, in particular drugs acting on the cholinergic system. Indeed, muscarinic agonists and antagonists play an important role in gastrointestinal function: digestive acetylcholine muscarinic receptor activation leads to smooth muscle contraction and exocrine secretion.

Long term digestive effects after *in utero* exposure to drugs acting on the cholinergic system may be all the more possible that (1) the majority of drugs with atropinic properties cross the placenta and (2) the cholinergic system appears early during antenatal life; muscarinic responses to acetylcholine have been detected in the heart from the 4th week post conception(5–8).

Many drugs, from various pharmacological classes, are competitive antagonists of cholinergic muscarinic receptors(9). This antagonist effect is called atropinic property. It is sometimes used to treat diseases like asthma, allergy and urinary incontinence. Nevertheless, it is mostly a side property that can cause digestive side effects through a decrease in both the peristalsis and the secretions, which can lead to constipation, abdominal pain or even intestinal atony and bowel obstruction. Digestive disorder in the fetus or the new born have already been widely describe in both animals and human (10–15). Exposure to several atropinic drugs may increase the atropinic burden and the intensity of atropinic side effects(16).

Thus, it may be possible that *in utero* exposure to drugs with atropinic properties during the development of the cholinergic system participate to the future onset of digestive disorders. This hypothesis has never been studied before.

The purpose of this study was to assess the risk of digestive medications use in early childhood (0-3 years old) associated with *in utero* exposure to atropinic drugs (exposure status and exposure intensity). The secondary analysis aimed at investigating the association between *in utero* exposure to atropinic drugs and each type of digestive disorders (constipation, diarrhea, vomiting or gastroesophageal reflux disease and gastro-intestinal pain).

2. METHODS

2.1 STUDY DESIGN

This observational cohort study compared the number of digestive disorders occurrences between two groups of children: one group exposed *in utero* to atropinic drugs and one unexposed group.

2.2 DATA SOURCE

The cohort POMME (*PrescriptiOn Médicaments Mères Enfants*¹) was used to carry out this study. POMME is a French cohort implemented in 2011 to evaluate the long-term effects of *in utero* exposure to drugs.

Children recorded in POMME are born between the 1st of July 2010 and the 30th of June 2011, to women covered by the Health Insurance System in Haute-Garonne (south-west France). POMME provides anonymous medical data about mothers and children. POMME yearly collects, from CPAM, anonymous data about prescribed and reimbursed drugs and medical care to the children. Thus, POMME holds information about drugs reimbursed to children during prenatal life (from conception) and infancy.

2.3 PARTICIPANTS

The population consisted of all children having reached 3 years of age included in POMME. Children who died before 3 years of age and those with a digestive birth defect were excluded for the comparative

¹ Mothers and children drug prescriptions

analysis but not for the descriptive analysis to ensure that *in utero* exposure to atropinic drugs was not associated with more deaths before 3 years of age or with digestive birth defects.

2.4 EXPOSURE STATUS

The exposure was defined as the dispensation of at least one atropinic drug to the mother during pregnancy (prenatal exposure).

A list of drugs with atropinic properties, drawn up by Beau *et al.*(17), was used to determine the children exposure status. This list included atropinic drugs and assigned them an atropinic score based on the lists of Duran(18), Laroche(19) and the ANSM (*Agence Nationale de Sécurité du Médicament et des produits de santé*²)(20). This list has been updated for the present study(21).

Firstly, each prescribed and dispensed drug was assigned its atropinic score: 0 (null), 1 (low) or 3 (strong). Secondly, atropinic burden during pregnancy was calculated by adding the atropinic scores of drugs the children were prenatally exposed to. Thirdly, children were classified into four groups according to their atropinic burden exposure during antenatal life: 0 (unexposed children), [1-3[, [3-9[and ≥ 9 .

The intensity of the exposure was also estimated by the duration of exposure to atropinic drugs during antenatal life: it was appreciated by the number of different dates when pregnant women were reimbursed for atropinic drugs.

2.5 OUTCOMES

The main studied outcome was the number of periods of digestive disorder drug uses in early childhood (0-3 years). The use of these medications was considered to reflect digestive disorders which were severe enough to consult a physician. The ATC (Anatomical Therapeutic Chemical) classification was used to select digestive disorder medications: hence, prescriptions of drugs for acid related disorders (A02), drugs for functional gastrointestinal disorders (A03), antiemetics and antinauseants (A04), laxatives (A06) and antidiarrheal, intestinal antiinflammatory/antiinfective agents (A07, except class A07A: Intestinal antiinfectives). Oral rehydration salt formulas were also included in the list of antidiarrheal medications. Subsequently, all digestive medications were classified into four categories: drugs for constipation (ATC A06), diarrhea (ATC A07), vomiting or gastroesophageal reflux disease (ATC A02 and A04) and gastro-intestinal pain (ATC A03).

² National agency for drug safety

2.6 POTENTIAL CONFOUNDING VARIABLES

Potential confounding factors likely to be associated with digestive drug use in childhood were identified in the cohort. Regarding the mother, characteristics such as age at delivery, parity and work situation were considered, as well as presence of pathologies during pregnancy (diabetes, hypertension, pre-eclampsia and preterm labor). We also considered the number of different drugs dispensed to the mother during pregnancy, multiple pregnancy and smoking during pregnancy. Finally, confounding factors considered for children were gender, prematurity (pregnancy duration strictly lower than 245 days), an Apgar score lower than 7 at 1 and 5 minutes, pathologies during the first week of life, breast-feeding status, diagnosis of major congenital anomaly, eczema and metabolic disease.

2.7 STATISTICAL ANALYSIS

Continuous variables were defined as means (\pm standard deviation) while qualitative variables as absolute number and percentages. The first step was to describe prenatal exposure to atropinic drugs. Then, multinomial logistic regressions were used to compare maternal and child characteristics according to the exposure status (atropinic burden = 0, [1-3[, [3-9[, \geq 9).

Association between *in utero* atropinic burden and number of periods of digestive disorder drug use was evaluated using a Poisson model incorporating corrections for overdispersion (22,23).

Analyses were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA). A value of $p < 0.05$ was considered statistically significant.

2.9 ETHICS COMMITTEE APPROVAL

The study was approved by the French Data Protection Agency (CNIL, DR-2013-060)

3. RESULTS

The 8,372 children of the POMME cohort were included in this study (fig 1). Among them, 2,652 (31.7%) were prenatally exposed to atropinic drugs. Seventeen children met the exclusion criteria (death before 3 years of age and digestive birth defect) (fig 1). The number of deaths before 3 years and of digestive birth defects was not statistically different between exposed and unexposed children ($p=0,083$ and $p=0,860$ respectively).

3.1 POPULATION DESCRIPTION

Considering all the studied population, the average atropinic burden during pregnancy was 0.9 (± 2.3) and the average atropinic burden *per prescription* was 0.1 (± 0.4 ; max = 9). Among all women exposed to atropinic drugs during pregnancy, the average atropinic burden was 2.9 (± 3.3 ; max = 54). Around 40% of exposed women received at least one drug with strong atropinic properties (score = 3). The distribution of women according to the exposure status was 16.6% (N = 1,386) in the group of atropinic burden [1-3[, 13.8% (N = 1,152) in the group of atropinic burden [3-9[and 1.4% (N = 114) in the group of atropinic burden ≥ 9 .

Women received atropinic drugs mostly during early pregnancy. More than 21% (N = 1,815) received at least one atropinic drug during the first trimester of pregnancy, 10.3% (N = 860) during the second one and 8.0% (N = 673) during the third one.

The most prescribed drugs with atropinic properties belonged to the ATC class A (Alimentary tract and metabolism). Almost 70% of all exposed women received at least one atropinic drug of class A. Within this category, prokinetic drugs, like domperidone, were the most prescribed. In the second place we found atropinic drugs belonging to ATC class R (Respiratory system), which were used by one quarter of the exposed women. They were mainly antihistaminic drugs.

The most prescribed drugs with strong atropinic properties (score=3) were metopimazine (8.6%), oxomemazine (2.1%) and mequitazine (1.0%). As regards to the drugs with few atropinic properties, domperidone (13.2%), cetirizine (3.7%) and codeine (2.9%) were the most prescribed.

Women characteristics according to atropinic exposure status are reported in table 1. Women exposed to atropinic drugs were more likely to be older, to have more children, to be unemployed, to receive more different active substances during pregnancy and to breastfeed their children compared to unexposed women. Atropinic burden was also associated with short gestational age.

More than 90% of the children received digestive disorders medications between 0 and 3 years. It was mainly to treat diarrhea (80.4% of the children exposed) and vomiting or gastroesophageal reflux disease (76.1%). About a third (35.7%) of the children used drugs for gastro-intestinal pain and 16.7% used medications for constipation.

3.2 ATROPINIC EXPOSURE STATUS AND DIGESTIVE DISORDER MEDICATIONS

The numbers of episodes of digestive disorder medications use according to atropinic exposure status are presented in table 2. The number of digestive disorder episodes was statistically different between exposed and unexposed children ($p < 0.0001$). Exposed children had on average one more period of digestive medication intake (5,0 *versus* 4,0) between 0 and 3 years. Among the exposed group, the number of digestive disorders statistically differed according to atropinic burden *in utero* ($p < 0.0001$). This difference was observed in each category of digestive disorder.

In utero exposure to atropinic drugs was associated with an increase in the risk of treated digestive disorder occurrences (relative risk 1.11; 95% confidence interval 1.06 -1.16) between 0 and 3 years (Table 3).

Table 3 provides crude and adjusted relative risks for associations between *in utero* atropinic exposure intensity and digestive medication intake in early childhood. The risk of digestive drug use in infants increased with both the atropinic burden *in utero* and the number of different dates when pregnant women were reimbursed for atropinic drugs ($p < 0.05$).

3.3 ATROPINIC EXPOSURE AND DIFFERENT TYPES OF DIGESTIVE DISORDERS

Crude and adjusted relative risks for associations between *in utero* exposure to atropinic drugs and each type of digestive disorder are presented in table 4. Drugs for constipation and gastro-intestinal pain occurrences were not statistically different between exposed and unexposed children. *In utero* exposure to atropinic drugs was significantly associated with an increase in diarrhea occurrences in breastfed children. The association was not significant in non-breastfed children. An adjusted analysis also showed an association between *in utero* exposure to atropinic drugs and vomiting or gastroesophageal reflux disease.

4. COMMENTS

More than 30% of the children were prenatally exposed to atropinic drugs. They had significantly more intake of medications for digestive disorders (5.0 *versus* 4.0) between 0 and 3 years than unexposed children. The strength of the association increased with both the atropinic burden and the number of different dates of atropinic drug dispensations. *In utero* exposure to atropinic drugs was significantly associated with occurrences of diarrhea and vomiting or gastroesophageal reflux disease. To our knowledge, this is the first study to

document that *in utero* exposure to drugs with atropinic properties is associated with a higher prescription of drugs that reflect digestive disorders.

The cholinergic system plays an important role in gastrointestinal function and atropinic drug administration often induces digestive side effects such as constipation. This is widely described in the elderly (24).

Our results showed that exposure to atropinic drugs during pregnancy, even in early pregnancy, might also cause digestive effects, which increase with the atropinic burden. The impact of the use of several drugs exhibiting the same pharmacodynamical effect has already been studied with other drugs. For example, Matok *et al.* have showed an increased risk of congenital malformations associated with exposure to different folic acid antagonists during the first trimester of pregnancy (25).

Delayed effects following fetal exposure to drugs or substances have already been identified. For example, some studies showed that fetal exposure to antiepileptic drugs was associated with neurodevelopment disorders(26–30). *In utero* exposure to Diethylstilbestrol has also been associated with an increased risk of cancer(31,32). Finally, Cantaloube *et al.* related that intrauterine exposure to potentially immunosuppressive drugs could be associated with an increased susceptibility to infections in early childhood (33). Other long term effects after *in utero* exposure to atropinic drugs have already been studied: Beau *et al.* looked into the consequences of antenatal exposure to atropinic drugs on child development and showed that atropinic drugs during pregnancy were associated with fewer cognitive acquisitions at 24 months (17). At least, childhood digestive disorders after *in utero* drug exposure were identified with other drugs than atropinics: Nijenhuis *et al.* showed that *in utero* exposure to selective serotonin antidepressants may disturb development of the enteric nervous system, resulting in a greater use of laxatives(4).

The observed digestive effects after exposure to atropinic drugs during antenatal life are biologically plausible. The gastrointestinal function is largely controlled by the cholinergic system: the activation of M1, M2 and M3 muscarinic receptors leads to an increase in both the intestinal peristalsis and the gastric and intestinal secretions. It is known that long term exposure to antagonists may induce receptor up-regulation (34–36). This has been observed after chronic treatment with muscarinic antagonists and the increase in receptor number was generally accompanied with augmented muscarinic acetylcholine receptor responsiveness (37). A possible explanation for our results is that muscarinic receptor blockade during the implementation of the fetal

cholinergic system might increase the number and/or the sensitivity of the cholinergic receptors, leading to long term digestive effects. This is supported by the fact that we found an association between *in utero* exposure to atropinic drugs with prescription of drugs for diarrhea or vomiting or gastroesophageal reflux disease and not with constipation; whereas atropinic drugs are known to cause constipation due to their pharmacological action. Furthermore, we observed an effect on digestive disorders that lasted for several years, but that tends to decrease over time.

Several limitations of this study should be noted. First, our study suffers from some methodological insufficiencies inherent in a pharmacoepidemiological study. The POMME cohort only provides data on drugs that were prescribed, delivered and reimbursed to outcare patients. We could not know whether drugs dispensed were effectively consumed by the mother and/or her child. Information on use of over-the-counter drugs and on drugs prescribed during hospitalization were not available. However, this might only slightly limit the interpretation of the results: indeed, regarding maternal exposure to atropinic drugs during pregnancy, although some atropinic drugs are available without prescription (for example Cimetidine), the vast majority needs a prescription to be dispensed, particularly those with strong atropinic properties. Moreover, if some women in the considered population received atropinic drugs during hospitalization, it may not limit the possibility to generalize the results, given the short duration of the exposure. Regarding digestive disorder medications taken by children, the use of over-the-counter drugs might be limited in such a young population. Furthermore, only few children probably received prescriptions of drugs for digestive disorders during hospitalization. A second limitation is that we assigned a score of 3 to drugs with strong atropinic properties and a score of 1 to drugs with few atropinic properties. Although this scale has been validated, we cannot completely ensure its clinical relevance. In addition, this scale does not take in consideration drug dosage. Nevertheless, many authors have already used this scale and we considered that it was the most appropriate for this study. Furthermore, atropinic burden was calculated by adding the atropinic scores of drugs used during pregnancy. We cannot be sure that this atropinic burden accurately reflects the muscarinic receptor blockade during antenatal life.

Finally, the third limitation is due to the potential unmeasured or insufficiently measured confounding factors that may have influenced the results. The population of women exposed to atropinic drugs during pregnancy received generally more drugs (atropinic or not) during pregnancy than the unexposed population. We cannot rule out the possibility that the number of drugs during pregnancy might influence childhood digestive disorders. One of the reasons could be the propensity of mothers who take a lot of medications to ask for more medicines for their children. A sensitivity analysis conducted on the subjects not exposed to atropinic drugs

showed a statistically significant effect of the number of different drugs (without atropinic property) dispensed to the mother during pregnancy on childhood digestive disorders. Therefore, our statistical models have been adjusted on the number of different drugs dispensed to the mother during pregnancy. The relative risk for the association between *in utero* exposure to atropinic drugs and digestive medications intake occurrences in childhood was 1.25 (95% confidence interval: 1.20 -1.31) without adjustment and decreased to 1.11 (95% confidence interval: 1.06 -1.16) when the statistical model was adjusted on the number of different drugs dispensed to the mother during pregnancy. Then, the adjustment on a variable that reflects the maternal behavior toward medicine intake mitigates the effect of the antenatal exposure to atropinic drugs on childhood digestive disorders but does not remove it. Other unmeasured confounders could have influenced the results. For example, we did not have access to data on child care arrangements. Nevertheless, one of the strengths of this study is that our models were adjusted on all the potential confounding factors available in POMME (i.e. mother characteristics and conditions and children characteristics). Moreover, we performed an additional analysis considering children antibiotic therapies, known to cause diarrhea. This additional adjustment failed to change the results of the effect of *in utero* atropinic exposure on infant digestive disorders. This contributes to ensure the robustness of our results. In addition, although the risk we measured is quite low, the impact of prenatally exposure to atropinic drugs might be clinically significant since digestive disorder are frequent in children.

Another strength of this study is that we used POMME, an innovative cohort, unique in France, which provides data about *in utero* exposure to drugs and children health status. It includes data for many children (more than 8,000), allowing comparative studies with a control group. So far, this is the first study to evaluate the risk of childhood digestive disorders after *in utero* exposure to drugs with atropinic properties. We found a significant association that increased with atropinic burden, supporting the plausibility of our results.

Further studies investigating for example cardiac or urinary long term effects of *in utero* exposure to atropinic drugs might provide useful information to improve the knowledge of the long term effects profile of atropinic drugs.

5. CONCLUSION

In conclusion, our study shows an association between fetal exposure to drugs with atropinic properties and an increased use of medications for digestive disorders in early childhood.

It is known that the causes of childhood digestive disorders are multifactorial (infections, inflammatory bowel diseases, genetic susceptibilities and psychological, socio-environmental factors...). While the relative risk for the association between *in utero* exposure to atropinic drugs and the occurrence of childhood digestive disorders is low, it suggests that muscarinic receptors blockade during the implementation and development of the digestive tract is also a risk factor for gastrointestinal disturbance in early childhood. The biological plausibility supports this result. This is an important consideration in view of the rather high number of drugs exhibiting this property. This study highlights long-term effects after *in utero* exposure to drugs.

Prescribers should be aware that drugs with atropinic properties are potentially inappropriate medications for the pregnant women and their children. Atropinic drugs that are not indispensable should be avoided during pregnancy. Otherwise, their use is possible but it would be advisable to pay attention to limit the association of drugs which share these atropinic property in order to reduce the atropinic burden *in utero*.

In practice, some digestive disorders in early childhood could be (at least partly) the consequence of a prenatal exposure to atropinic drugs. It is reassuring to know that the effect might lessen when the child will grow up.

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Compliance with Ethical Standards

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Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval This study was performed on anonymised patient data and ethics committee approval was therefore not required.

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