# The use of teratogenic medication during pregnancy and congenital anomalies of the offspring in the Northern Netherlands, 1981-2018

***Update: February 2020***

## Background

Medication use during pregnancy might be necessary, for example in patients with epilepsy. However, prescribed medications are not always safe during pregnancy. There are several classification systems for the safety of medication during pregnancy. Nowadays in Europe and the United States, descriptive text is used, instead of the formerly used letter classification A t/m D and X. For drugs that might lead to congenital anomalies in the offspring, the Dutch Teratology Information Service (TIS) uses:

1. Teratogen effect, outweigh benefit and risk, if necessary: monitor on adverse effects
2. Teratogen effect, do not use (temporarily)

For some of the medications in the second group, *teratogen effect, do not use (temporarily)*, a Pregnancy Prevention Program (PPP) has been set up.

Eurocat collects data since 1981 about possible risk factors for congenital anomalies. Parents fill in a questionnaire, which results in information about the use of medication by the mother during pregnancy, of the father during periconception, as well as information about chronic diseases, special health issues during pregnancy and lifestyle factors. Additional data about prescribed medications is collected from pharmacies. For this report we yearly investigate the Eurocat database to find out if and how many teratogenic medications were used by the mothers, and investigate which anomalies have occurred in the exposed offspring.

## Method

From the Eurocat database, all cases born between 1981 and 2018 were selected. We identified all cases that were exposed in utero to a medication described with 'teratogen effect' according to the TIS classification, or having a Pregnancy Prevention Program (PPP).

Mothers who used medication from category 1 (table 1), category 2 (table 2), or with a PPP (table 3) were counted.
A mother could occur in more than one medication group. Frequency tables are given for medication use in every medication group. Cases exposed to medications used in the second or third trimester only from categories 1 and 2 were excluded. All exposures to medications with a PPP were counted.
The Fisher's exact test (two sided) was used for associations on the level of the main groups of congenital anomalies of the offspring and teratogenic medication of the mother (SPSS Statistics, version 23). Associations were with a p-value less than .05 were considered significant. Medications with a count less than 5 were excluded from the test. Cases with multiple congenital anomalies are counted for in more than one anomaly group.

*Table 1. Medication from category 1: 'Teratogen effect, outweigh benefit and risk, monitor on adverse effects'*

| Medication name | Group |
|---|---|
| **Valproic acid*, carbamazepine, phenytoin, topiramate** | Antiepileptics, other |
| **Phenobarbital , primidone** | Antiepileptics, barbiturate class |
| **Carbimazole, propylthiouracil,thiamazole** | Thyreostatics |
| **Lithium** | Bipolar disorder treatment |

**additional advice TIS: 'Try to avoid the use of Valproic acid in pregnancy'.*

*Table 2. Medication from category 2: ' Teratogen effect, do not use (temporarily)'*

| Medication name | Group |
|---|---|
| **(dihydro)ergotamine** | Antimigraine |
| **Acenocoumarol, warfarin, fenprocoumon** | Anticoagulation |
| **ACE-inhibitors** | Cardiovascular treatment |
| **ATII-antagonists** | Cardiovascular treatment |
| **Tetracycline antibacterials** | Antibiotics |
| **Aminoglycoside antibacterials** | Antibiotics |
| **Kinine** | Antimalaria |
| **Nandrolone** | Anabolic steroid |
| **Cyproterone, danazol, tamoxifen** | Antihormones |
| **Methotrexate** | Antirheumatics |
| **Fluorouracil** | Cytostatics |

*Table 3. Medication with a Pregnancy Prevention Program*

| Medication name | Group |
|---|---|
| **Isotretinoin** | Antiacne |
| **Acitretinoin** | Antipsoriasis |
| **Thalidomide** | Antileprosy/antitumor |
| **Lenalidomide, pomalidomide** | Multiple myeloma |
| **Alitretinoin** | Severe eczema |
| **Ambrisentan, bosentan, macitentan (*)** | Pulmonary arterial hypertension |
| **Vismodegib** | Basal cell carcinoma |
| **Mycofenolic acid** | Immunosuppressant |

*(*) PPP due to maternal risks due to underlying illness*

## Results

In the period 1981-2018, 17,821 cases are registered at Eurocat. We discarded cases with a known cause, for example chromosomal anomalies, and cases with no information about medication use, leaving 10,899 cases.

Medication of category 1 and 2 was counted 298 times in total. Medication with a PPP was counted only once. For each group we counted the following numbers (table 4).

*Table 4. Number of cases exposed to medication from category 1 and 2, or with a PPP Eurocat database 1981-2018*

| Medication name | | N |
|---|---|---|
| *Category 1* | *Total count* | *87* |
| **Valproic acid, Carbamazepine, Phenytoin, Topiramate, Phenobarbital, Primidone (all antiepileptics)** | | **72*** |
| *Valproic acid* | | *41* |
| *Carbamazepine, Phenytoin, Topiramate* | | *31* |
| *Phenobarbital, Primidone* | | *4* |
| **Carbimazole, Propylthiouracil, Thiamazole** | | **9** |
| **Lithium** | | **6** |
| *Category 2* | *Total count* | *211* |
| **Tetracycline antibacterials** | | **177** |
| **Acenocoumarol, Warfarin, Fenprocoumon** | | **18** |
| **(dihydro)Ergotamine** | | **5** |
| **ACE-inhibitors** | | **6** |
| **Methotrexate** | | **1** |
| **Angiotensin II-antagonists** | | **4** |
| **Aminoglycoside antibacterials** | | **0** |
| **Kinine** | | **0** |
| **Nandrolone** | | **0** |
| **Cyproterone, Danazol, Tamoxifen** | | **0** |
| **Fluorouracil** | | **0** |
| *Pregnancy Prevention Program* | *Total count* | *1* |
| **Isotretinoin** | | **1** |
| **Acitretinoin** | | **0** |
| **Thalidomide** | | **0** |
| **Lenalidomide, Pomalidomide** | | **0** |
| **Alitretinoin** | | **0** |
| **Ambrisentan, Bosentan, Macitentan** | | **0** |
| **Vismodegib** | | **0** |
| **Mycofenolic acid** | | **0** |

*Some mothers used a barbiturate as well as another antiepileptic.

Congenital anomalies in the main groups were counted 12,039 times in total. For each main anomaly group we counted the following numbers (table 5).

*Table 5. Main congenital anomaly groups, Eurocat database 1981-2018*

| Main anomaly group | N |
|---|---|
| *Total count* | 12,039 |
| **Anomalies of the nervous system** | **870** |
| **Eye anomalies** | **232** |
| **Ear anomalies** | **69** |
| **Congenital heart defects** | **2898** |
| **Congenital malformations of the respiratory system** | **249** |
| **Oro-facial clefts** | **979** |
| **Congenital malformations of the digestive system** | **1333** |
| **Genital anomalies** | **852** |
| **Congenital malformations of the urinary system** | **1284** |
| **Limb anomalies** | **3092** |
| **Abdominal wall defects** | **181** |

For each group of teratogenic medication, we compared exposed cases from a specific anomaly group with all other cases not exposed to this specific teratogenic medication. Total number of cases is 10,899. As mentioned before, a mother could occur in more than one medication group and cases with multiple congenital anomalies cover more than one anomaly group. The result of significant associations are shown in table 6.

*Table 6. Number of Category 1 and 2 medication associated with specific main congenital anomaly groups, Eurocat database 1981-2018*

| | **Anomalies of the nervous system** | | |
|---|---|---|---|
| Exposed to medication **category 1**: | | | |
| | n | expected count | p-value |
| Valproic acid, Carbamazepine, Phenytoin, Topiramate, Phenobarbital, Primidone (n=72) | 16 | 5,7 | <.001 |
| *Valproic acid (n=42)* | 11 | 3,3 | <.001 |
| Exposed to medication **category 2**: | | | |
| ACE-inhibitors (n=6) | 3 | 0,5 | .008 |
| | | | |
| | **Anomalies of the respiratory system** | | |
| Exposed to medication **category 1**: | | | |
| Carbimazole, Propylthiouracil, Thiamazole (n=9) | 2 | 0,2 | .017 |

We found an –well known from literature- association between the use of antiepileptics and anomalies of the nervous system (16, expected count 5,7, p<.001). In more than half of the cases (41 out of 72), valproic acid was used. We therefore also found an association between valproic acid only and anomalies of the nervous system (11, expected count 3,3, p<.001).

ACE-inhibitors were also associated with the nervous system anomalies (3, expected count 0,5, p=.008).

In the small group of thyreostatics (carbimazole, propylthiouracil and thiamazole), we found an association with anomalies of the respiratory system (2, expected count 0,2, p=.017). Both cases have lung hypoplasia.

The largest group is formed by the tetracycline antibacterials. We found no statistically significant associations in this group. Apart from the above mentioned associations, we found no significant signals in category 1 and 2 medications.

Only one case was exposed to a medication that nowadays has a PPP. The mother used isotretinoin in the year 2000 and the child suffered from a mild urinary tract anomaly.

## New in this report

We found a total of 260 new cases with maternal medication use in 2018. Only five new cases concerned medication with a possible teratogen effect. Within the group of antiepileptics, we count one new case with maternal use of valproic acid. Also in the group of ACE-inhibitors, we found one new case. The associations found within these two groups are thus more significant, compared to the last year report.

The other three new cases with maternal medication use with possible teratogen effect in 2018, concerned one child exposed to tetracycline antibacterials, one exposed to anticoagulation agents and one exposed to angiotensin II-antagonists. In these three medication groups, no significant associations with congenital anomalies were found.

## Comments

Our yearly check on the use of medications with a possible teratogen effect, results in more or less stable outcome of known cases. After 2000, no more cases exposed to a medication that nowadays has a PPP, were found in our region.