Correlation of maternal expositions during pregnancy with three, foetal gastrointestinal tract developmental anomalies

Doctoral thesis

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Introduction

Recognition of congenital anomalies at birth is the most unexpected and tragedic event of an obstetrician's everyday practice. Setting up intrauterine diagnosis in time is a natural demand from professionals, pregnant women and society. This question gets its actuality from the liberalisation of abortion law over the 12th week, in case of congenital anomalies. The underlying causes of pathogenesis of developmental anomalies – justified by several studies – are mainly genetical, but it is also affected in high percentage by maternal expositions during pregnancy.

Congenital anomalies (CA), in a broader sense, are all those abnormal conditions, which are present at birth, being detected during pregnancy or after birth. CA includes those genetical anomalies, which might be manifested in adulthood, but in the practice of the obstetrician it mainly means the morphological deviancies.

Public health and sociological significance of CA is determined by the severity and prevalence of cases . CA with a 6-7% prevalence, and thank to the prenatal diagnostics with a 3-5 % prevalence by birth are still a leading cause of perinatal mortality. In 15 % of early abortions , in 50 % mature stillborns there is a CA as an underlying cause, but those babies, who survive, have adaptation difficulties , which is mostly caused by insufficient intrauterine growth. Mostly the morphological anomalies cannot be completely restored, , that is why the potential underlying causes and primer prevention is inevitable.

First level prevention, which is hindering of the occurrence of the anomaly, is followed by secunder prevention. Secunder prevention, in this case means abortion, if the anomaly is incompatible with life and it is recognised earlier than the 24th gestational week. In the current Hungarian law, in case of proved CA the pregnancy can be terminated in any time. Although if the anomaly is progressive an operable at the same time, it worths to consider the operation at that time of prematurity, when the baby is already able to survive. Tertier prevention means the hindering of deteroriation of the already developed case, and prevent the complications.

Based on prevalence CA are grouped into classes, which correlate with he severity. Frequent anomalies occure in 0,1 thousandth are Down-syndrome, congenital dislocated hip, inguinal hernia, orchidopexy, ventral septum defect, hypospadiasis, hare-lip, open spine, stenosus pylori. 25 diseases hava prevalence of 0.1-0.99 thousandth. The other 3000 publicated cases mean the rare category, lower than 0.1 thousandth prevalance.

In the classification of CA the most cases are minor anomalies. Minor anomalies do not affect the quality of life, and can be described as a normal variant, if it is isolated. They have clinical significance occuring simultanously together to indicate a more severe condition or syndrome. Mild and severe anomalies are classified based on the amount of needed intervention. Those anomalies which are incompatible with life are really rare.

Pathophysiology of CA are mainly well-known. Malformation is the pathological development both with inherited and aquired genetic underlying cause. Disruption is the primarily normally developing organ's injury caused by teratogenic reason, while the deformation is a rare, maternal, mechanical injury of the normally developing organ. In summary the underlying causes may be genetical, chemical-biological-physical or multifactorial.

An anomaly is isolated, when the lesion affects one organ or organ system. Multiplex diseases affect more, independent organs. Special form is the syndrome, which means more, seemingly independent, but almost every time together occuring congenital anomalies.

Aims

The aim of our study is -using the NRCA database- to assess and analyse the correlation between three congenital anomalies affecting the gastrointestinal tract (isolated oesophageal atresy, infantile hypertrophic stenosis pylory and isolated anorectal malformation) and maternal factors during pregnancy. Our study was based on prenatal care documents , whether maternal acute and chronic diseases and medicines , which treat these conditions have any effect on developing IOA, IHPS and IARM. We had special attention on folic acid, since its effect was well-known on the development of other malformations. Furthermore we wanted to analyse the social-demographic background. Our questions were the followings:

1. Are the developmental disorders of the fetal GI system influenced by the maternal social status?
2. What kind of maternal diseases (acute and chronic) possibly have an effect on the cases of IOA?
3. What kind of maternal medicine-expositions possibly have an effect on the cases of IOA?
4. What kind of maternal diseases (acute and chronic) possibly have an effect on the cases of IHPS?
5. What kind of maternal medicine-expositions possibly have an effect on the cases of IHPS?
6. What kind of maternal diseases (acute and chronic) possibly have an effect on the cases of IARM?
7. What kind of maternal medicine-expositions possibly have an effect on the cases of IARM?
8. Has (taken) Folic acid any effect on the formation of developmental disorders of the fetal GI system?

Methods

National Registry of Congenital Anomalies (NRCA)

NRCA was launched in 1962. It is the first database, in which the whole population's congenital anomalies are registered . Based on the suggestion of Jenő Sárkány MD, the then director-general of Heim Pál Children's Hospital, the Ministry of Health let commit doctors to register the congenital anomalies until the children's one year of age. Maintaining the registry was the task of Czeizel Endre MD from 1970, who put emphasise on following the WHO guidelines.

Since the report has been mandatory, it has been very effective to register the CA in Hungary. Most of these cases are reported by obstetricians and pediatricians, since birth givings are hospitalised in Hungary, observed by an obstetrician-gynecologist, and medical attendance is performed by the lovely pediatricians. Besides , those pediatric institutes, which take part in the therapy and medical attendance of these cases have a great part in report.

In case of neonatal death the autopsy was mandatory, while in case of stillbirth it happened in 80 % of cases. These results, as far as they proved congenital anomalies were registered. Since 1984 fetal diagnostic centers also supply data, independently of the outcome of pregnancy. Based on every registered cases between 1980 and 1996, the prevalence of congenital anomalies was 35 cases out of 1000 cases, and 90 % of the anomalies were registered in the NRCA.

Mandatory to register.

1. Obstetrical institutes, where children born with anomalies
2. Pediatric institutes, where children with anomalies are treated
3. Pathology institutes, where the autopsies are performed and the autopsy documents are sent to the NRCA
4. Since 1984 the prenatal diagnostic centers

Followed by parental demand, the NRCA institute organised meetings for children with congenital anomalies and their parents annually. The collegues of the institute shared every information about the anomalies, including the causes, the probability of recourrance. Two geneticist, who were specialised to this area, examined the parents and their children . The physical examinations helped to strengthen the diagnosis, and subclassify them.

Case control surveillance of developmental malformations (CCSDM)

Those congenital anomalies, including IOA, IHPS and IARM which met the criteria listed below were taken into the CCSDM.

1. In 3 months after birth or procured abortion it was claimed to the NRCA
2. The underlying cause was not gene mutation or chromosome-aberration
3. Those anomalies, which are not these three mild anomalies: congenital dislocated hip, congenital inguinal hernia and large haemangioma, since these do not have great clinical impact and their development is well-known

The control group was formed of newborns without congenital anomalies but had the same gender; their parents lived in the same geographical area, and were born on the same gestational week. As the examined group.

It is important to emphasize, that the CCSMD was founded in 1980, but the data hasn't been validated since 1997, when the data collecting was changed. This explains why data from the period 1980-1997 were examined. Data are from three sources:

1. Prospective, prenatal care documentation:

Mothers of the examined and the control group got letters from the institute, which explained the study and were asked to send the findings of them and their fetus', the findings they got during prenatal care and that information, which they had about the diagnostics of the congenital anomalies to the co-worker of the institute. The institute got the documents mainly in 4 weeks. Since the prenatal care is obligatory in Hungary, pregnant women visit the obstetrician from the 6th-8th gestational week during pregnancy approximately 7 times. The obstetricians' job was to document every problem, the type and exposure of the applied therapy during pregnancy.

2. Retrospective, based on the information given by mothers:

Questionnaires, information sheets and informed consent forms were sent to mothers right after the birth giving. The questionnaires were mainly about the diseases, drugs and food supplements taken during pregnancy. The average +/- SD time between the end of pregnancy and the arrival of the information package (including the prenatal care book, final reports,

questionnaires, consent information forms), which were sent in pre-stamped stationeries was 3.5 +/- 2.9 months in the examined group and 5.2 +/- 2,1 months in the control group.

3. Via complementary survey:

Postnatal caregivers visited those families personally, who did not answer to the request, helped them to fill the forms and summarised the documentation of the prenatal care. This way of collection of information was disapproved by the Research Ethic Committee, thus the postnatal caregivers could have visited 200 non-answering and 600 other mothers 96.3 % of the cases with congenital anomalies gave the needed information (84.4% via questionnaires, 11.9% via the visit of postnatal care-givers) and 83% of the control group answered (81.3% via questionnaires and 1.7 % via the visit of the postnatal caregivers). Since 98% of the mothers signed the consent information form, only by 2 % were the personal data destructed.

Results

In the IOA group based on the data of CCSDM 221 IOA cases occurred 1980-1996 in Hungary. One of the patients with IOA was stillborn and none of them were prenatally diagnosed. Out of the 220 live birth cases 30 (13.6 %) were examined in the NRCA by the parental meetings and 356 cases were involved in the case control group. although originally to every case there were two control cases ordered, this proportion was 1.0:1.8 because of the non-answering cases. 1980-1986 there were 2 138 151 living birth in Hungary, which were represented by a population-control group of 38 151 cases and that was the 1.8% of the births. The distributions in the parity of the mothers showed a significant difference, primiparous were more represented amongst those involved.

According to the data about occupation, we recognized that amongst the involved there were more people living under worse sociological circumstances. Mothers with third-level education or senior position occurred by lower proportion (32.6%), whereas this proportion was 42.4% in the case-control group and 38.5% in the population control group. Corresponding to this, the proportion of the uneducated, manual worker or housewives was higher (33.9%) than in the control group (28.4%) or into the population-control group (28.0%).

From the acute diseases only the upper airway infections meant higher risk for IOA. Out of these 7 cases 4 mothers had tonsillitis and the other three had sinusitis, laryngitis or bronchitis during pregnancy.

From the chronic diseases only the essential high blood pressure was more frequent , it occurred in 22 cases (10.0%), while in the case-control group it occurred in 13 cases (3.7%, OR 95%, CI:2.1, 1.2-3.8). In the population control group essential high blood pressure occurred in 1579 cases (4.1%; OR 95% CI 2.4 1.6-3.8).

Regarding drug therapy only one drug, the nifedipin had casual link with the risk of developing IOA compared to the population control group (OR 95%CI 3,12 1,45-6,71), while taking folic acid did not have any effect in the critical period.

In the examined period there were 241 living birth cases of IHPS in the database of CCSMD. 206 cases (85.5%) out of 241 cases were boys. 357 cases were in the control-group, out of which 303 (84.9%) were boys.

Analysis of acute and chronic diseases of mothers was based on the prenatal care booklet, which was written by the doctor. While in case of acute diseases we did not find a causative relationship, the thyroid gland's malfunction occurred more often in the affected mothers. This occurs only in 4 cases, out of which was hyperthyroidism in 3 cases (1.2 %). Hyperthyroidism did not occur in the control group and was 0.4 % in the population-control group. By two mothers hyperthyroidism started before pregnancy and in one case it started in the 3rd month. These women did not require therapy.

Among the examined 22 drugs taken during pregnancy, only nalidix acid showed strong correlation with IHPS (OR 95%CI 6,53 3,03-14,06).

Out of 231 IARM cases registered in the NRCA 28 times (12.1%) were further tests performed at the time of the parental meetings in the NRCA institute. In these cases there was no stillbirth, and the IARM could have not been diagnosed intrauterine. Next to the 231 IARM cases 361 control cases were ordered. AS we lost some control case due to the low compliance, the ratio become instead of 1.0:2.0, 1.0:1.6. Population control group was formed 1.8 % out of those, who were born 1980-1996, which meant 38.151 people.

We observed, that the diseases, which occur during the critical period regarding the development of IARM do not have a significant effect on the prevalence of IARM. Except the gastrointestinal and urinary tract infections. From the case group 4 mothers had acute GIT disease; half of them had gastritis in the critical period. Out of 5 cases 2 mothers had cystitis, 2 had nephrolithiasis and one had nephritis.

Regarding the mother's chronic disease there were no difference between the groups.

Conclusions

Our analytic studies were based on the database of CCSDM, which includes a huge, homogenous Hungarian (Caucasian) population. All of the three studied congenital anomalies (IOA, IHPS, and IARM) diagnostic fidelity is really high, considering, that scientist worked with exact and in 1/10 of the cases, via parental meetings double-checked data. The diagnoses of the database of CCSDM were reassured in 3.5+-2.1 months. To conclude we examined every acute and chronic disease, every drug and food supplement of the pregnant women based on medical documentation, which proved us prospective medical data.

Although we worked with a reliable, big database and we applied mathematical analysis, there were opportunities for bias results. Those retrospective data, which were based on the mothers' memories could distort the results.

However after processing the whole database, we made these new conclusions:

1. The social state and parity of the mother had negative correlation with isolated oesophagus atresy.
2. Acute respiratory tract infections during pregnancy elevates the risk of IOA.
3. High blood pressure of the pregnant women treated with nifedipin elevates the risk of IOA.
4. Hyperthyroidism during pregnancy elevates the risk of IHPS.
5. Nalidix acid (Nevigramon) taken during pregnancy elevates the risk of IHPS.
6. The risk of IARM is elevated by UTIs of the pregnant women.
7. Folic acid taken during pregnancy do not lower the risk of these three diseases (on the other hand it lower the risk of other congenital anomalies).

Publications related to the thesis:

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