The efficacy of obstetric ultrasound in the diagnosis of congenital malformations of the fetus

doctoral thesis

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1. Introduction

Nowadays, ultrasound is the most important diagnostic technique in obstetrics, especially in the diagnosis of congenital malformations. It is important to know which malformations can be detected prenatally with a high certainty, and which anomalies can only be diagnosed partially or not at all before birth. High expectations of the parents, that all anomalies can be fully detected antenatally may lead to lawsuits in undiagnosed cases. Thus, it is indispensable for physicians to be up-to-date in the efficacy of obstetric ultrasound to be able to inform the parents properly. Prenatal diagnosis is also a huge responsibility for physicians as a false diagnosis may have immense consequences both for the fetus and the family. Therefore, it is important to examine that in what ratio and how early congenital malformations may be diagnosed in the current ultrasound examination protocol of the Hungarian prenatal care system.

2. Objectives

My objective was to examine the following:

1. How effective was ultrasound in diagnosing congenital malformations?
2. How frequently congenital malformations were associated with chromosomal abnormalities?
3. How frequently congenital malformations occurred as part of multiple malformations?
4. What was the birth prevalence of congenital malformations?
5. When (what gestational week) were congenital anomalies first detected? How many ultrasound examinations were conducted on average?
6. In what ratio congenital malformations were associated with intrauterine retardation?
7. How well Uncertainty and Difficulty Factors characterized the difficulties of diagnosing congenital anomalies?

3. Methods

In our study, the fetopathological/postnatal records were processed in those cases where congenital malformations were diagnosed between 2006 and 2012 at Semmelweis University`s 1st Department of Obstetrics and Gyneacology. Prenatal ultrasound records, postnatal clinical data and fetopathological findings were processed. I analyzed data of the fetuses: their weight, gestational age, maternal age at the time of birth/abortion, the number of ultrasound examinations performed, as well as the time of the detection of the abnormalities.

I investigated separately the anomalies associated with chromosome abnormalities and representing parts of multiple malformations. In the interest of literature data comparability, the anomalies were grouped considering the criteria of EUROCAT guidelines. We sorted the anomalies in 6 main groups:

- Craniospinal,
- Craniofacial,
- Thoracic,
- Abdominal and abdominal wall,
- Urogenital,
- Extremities.

I divided the cases in three groups: Group 1: prenatal ultrasonography and postnatal/fetopathological examinations gave totally equal results; Group 2: postnatally/post abortion discovered anomalies were partially detected in prenatal examinations; and Group 3: prenatal ultrasonography failed to detect any malformations

I considered an anomaly partially diagnosed, when an abnormality of a specific organ was detected with prenatal ultrasound, however the

postnatal/post-abortion examinations showed a different anomaly of the organ, or when the anomaly was not specified prenatally. For instance, when prenatally ventriculomegaly/hydrocephalus was detected, and the postnatal/ post-abortion examinations proved agenesis/dysgenesis of the corpus callosum. In other cases, the prenatally detected club foot was shown postnatally as arthrogryposis.
I also examined the occurrence of fetal hydrops and intrauterine retardation.

Ultrasound examinations were carried out in the Ultrasound Laboratory of the 1st Department of Obstetrics and Gyneacology. We have used Philips® HD 11XE (Philips Ultasound), GE Voluson® 730PRO (GE Medical System Kretztechnik GmbH & Co OHG), and Medison SA9900 ultrasound devices (Medison Co., LTD). The examinations were performed in accordance with the recommendations of FMF and the protocol developed by the Hungarian Society of Obstetric and Gynecological Ultrasonography.
Statistical analysis included determination of sensitivity. In calculating significance, the Chi-square ($\chi 2$) test was used. In case of $p<0.05$, the anomaly was considered statistically significant.

I introduced two new parameters to characterize the detectability of the anomalies. The Uncertainty factor is calculated by dividing the number of partially diagnosed cases with the sum of the partially and fully diagnosed cases.

$$F(B) = \frac{n(partially\ diagnosed)}{n(partially\ diagnosed) + n\ (fully\ diagnosed)}$$

The other parameter, the Difficulty factor is calculated by dividing the number of undiagnosed cases with the sum of the number of partially and fully diagnosed cases.

$$F(N) = \frac{n(undiagnosed)}{n(partially\ diagnosed) + n(fully\ diagnosed)}$$

The Uncertainty and Difficulty Factors were considered low when under 0.5, high, when between 0.5 and 1, and very high when 1 or higher.

4. Results

25700 infants were born, and 8580 pregnancies were terminated at the 1st Department of Obstetrics and Gyneacology, Semmelweis University between 2006 and 2012. Out of 8580 terminations, 5628 were induced, while 2952 were spontaneous. Most of the terminations happened in the first trimester (7453 cases, 4822 induced and 2631 spontaneous), while 1127 cases occurred in the second trimester (806 induced and 321 spontaneous). All together, 1616 fetuses were affected in congenital malformations in the 7 years examined.

We excluded 416 cases out of 1616, including the cases where no ultrasound examinations were carried out (68 cases, 61 births and 7 terminations). In seven of these cases, multiplex malformations were found. Also, in the 68 cases, 25 thoracic, 7 abdominal, 11 urogenital, 20 craniofacial anomalies and 7 malformations of the extremities were found. Four fetuses were affected by fetal hydrops. Further 348 cases were excluded when the fetuses were suffering from chromosomal abnormalities and minor anomalies, but no major congenital malformations were found. Therefore, out of 1616, we analyzed the data of 1200 fetuses.

Out of 1200 fetuses, 644 were boys and 515 were girls. In 41 cases, the gender was unknown. Average maternal age was 29.96±5.88 years at the time of delivery/abortion.

Out of 1200 pregnancies, 671 ended with birth, while 529 ended with termination (27 spontaneous and 502 induced).
In those cases when the pregnancy ended with delivery, the average gestational age was 35.26±4.2 weeks, and the average birth weight was 2408.67±944.41g. The data regarding the birth weight was missing in 8

cases, and in 3 newborns, gestational age was unknown. Out of 671 deliveries, 335 occurred before 37 weeks of gestation (49.93%).

The average gestational age at termination was 19.88±2.53 weeks. The average weight of the fetuses was 324.03±156.07g. However, this data was missing in 47 cases.

On average, 3.35±3.06 ultrasound examinations were carried out.
Out of the 1200 fetuses, 1129 were singular, 68 were gemini and 3 were trigemini. In 6 gemini cases, both fetuses were affected by congenital malformations. In all 3 of the trigemini cases, only one of the fetuses were affected.

Out of the 1200 fetuses, chromosomal abnormalities occurred in 73 cases: 37 cases of Trisomy 21 (Down syndrome), 20 cases of Trisomy 18 (Edwards syndrome), 6 cases of Trisomy 13 (Patau syndrome) and 2 cases of Turner syndrome. In 8 fetuses, other chromosomal abnormalities were found: triploidy in 2 cases, 1 case of Trisomy 9, 1 case of ring formation of the X chromosome, 1 case of deletion of Chromosome 1, and 3 cases of other anomalies.

In 211 fetuses, multiple malformations were found. Multiple malformations were associated with chromosomal anomaly in 22 fetuses, while 189 fetuses were euploid. In 133 of the 189 euploid cases, malformations only affected two organs. In 64 fetuses, the malformations affected 3 or more organs. In fetuses with multiple malformations, thoracic anomalies occurred the most frequently (49.74%, 94 cases).

Altogether, 1867 anomalies occurred in the 1200 fetuses: 351 craniospinal malformations, 135 face and neck abnormalities, 675 thoracic anomalies, 240 abdominal and abdominal wall malformations,

308 urogenital abnormalities and 158 malformations of the extremities and the bones.

To characterize the difficulties of the ultrasound diagnosis of congenital malformations, I introduced two new parameters: the Uncertainty and Difficulty factors.

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n the craniospinal group, Arnold Chiari malformation both had very high Uncertainty (1.0) and Difficulty factors (1.0). Furthermore, Difficulty factor was very high in case of microcephalia (1.67) and high in the agenesis/dysgenesis of the corpus callosum (0.73). Uncertainty and Difficulty factors of craniospinal malformations are shown in Table 1.

Table 1 Uncertanty F(B) and difficulty factors F(N)in the detection of craniospinal malformations

Type of anomaly		I.totally discovered		II. Partially discovered		III. Not detected		Uncertanty fact. F(B)*	Difficulty fact. F(N)*
	cases	n	%	n	%	n	%	II / I + II	III /I + II
ventriculomegaly/hydrocephaly	115	91	79.13%	6	5.22%	18	15.65%	0.06	0.19
agenesis/dysgenesis of the corpus callosum	26	13	50.00%	2	7.69%	11	42.31%	0.13	0.73
spina bifida*	72	64	88.89%	5	6.94%	3	4.17%	0.00	0.04
holoprosencephaly	26	19	73.08%	5	19.23%	2	7.69%	7.00	0.08
Dandy-Walker malformation/vermis hypoplasy	14	9	64.29%	2	14.29%	3	21.43%	0.00	0.27
microcephaly	8	2	25.00%	1	12.50%	5	62.50%	18.00	1.67
hydranencephaly	8	7	87.50%	0	0.00%	1	12.50%	0.00	0.14
sacrococcygeal teratome	8	6	75.00%	2	25.00%	0	0.00%	0.25	0.00
anencephaly/exencephaly	20	19	95.00%	0	0.00%	1	5.00%	0.00	0.05
encephalocele, meningocele	9	6	66.67%	1	11.11%	2	22.22%	0.14	0.29
Arnold-Chiari malformation	2	0	0.00%	1	50.00%	1	50.00%	1.00	1.00
other craniospinal anomalies	43	19	44.19%	12	27.91%	12	27.91%	0.39	0.39
Totals	**351**	**255**	**72.65%**	**37**	**10.54%**	**59**	**16.81%**	**0.14**	**0.29**

*<0.5 low ≥0.5 high ≥1 very high

We found high and very high Uncertainty and Difficulty factors in all malformation groups of the face and neck with a total Difficulty factor of 1.87 (Table 2). Both the Uncertainty (1.0) and Difficulty factors (13.0)

were very high in case of the choanal atresia group. Difficulty factor was very high in the micrognathia (11.0), other craniofacial malformations (2.88), microphthalmy/anophthalmia (2.0), and exophthalmia (1.00) groups. Difficulty factor was the lowest, but still high in the cleft lip and palate group (0.82).

Table 2 Uncertanty F(B) and difficulty factors F(N) in the detection of craniofacial malformations

Type of anomaly		I.totally discovered		II. Partially discovered		III. Not detected		Uncertanty fact. F(B)*	Diff. factor F(N)*
	cases	n	%	n	%	n	%	II / I + II	III /I + II
cleft lip and palate	60	32	53.33%	1	1.67%	27	45.00%	0.03	0.82
choanal atresia	14	0	0.00%	1	7.14%	13	92.86%	1.00	13.00
microphthalmy/anophthalmy	9	2	22.22%	1	11.11%	6	66.67%	0.33	2.00
absent ear	7	0	0.00%	0	0.00%	7	100.00%		
micrognathy	12	1	8.33%	0	0.00%	11	91.67%	0.00	11.00
exophthalmy	2	1	50.00%	0	0.00%	1	50.00%	0.00	1.00
other craniofacial	31	7	22.58%	1	3.23%	23	74.19%	0.13	2.88
összesen	**135**	**43**	**31.85%**	**4**	**2.96%**	**88**	**65.19%**	**0.09**	**1.87**

*<0.5 low ≥0.5 high ≥1 very high

Among thoracic abnormalities, Uncertainty factor was high in only four malformation groups: malposition of the pulmonary arteries (0.6), atrial septal defect (0.54), dilated right and left ventricle (0.5), and tuberous sclerosis (0.5). Difficulty factor was higher in the other lung malformations group (1.08). Uncertainty and Difficulty factor values of thoracic malformations are shown in Table 3.

Table 3 Uncertanty F(B) and difficulty factors F(N) in the ultrasound detection of craniofacial malformations

Type of anomaly		I.totally discovered		II. Partially discovered		III. Not detected		Uncertanty fact. F(B)*	Difficulty fact. F(N)*
	cases	n	%	n	%	n	%	II / I + II	III /I + II
atrial septal defect (ASD)	41	13	31.71%	15	36.59%	13	31.71%	0.54	0.46
ventricular septal defect (VSD)	126	68	53.97%	19	15.08%	39	30.95%	0.22	0.45
atrioventricular septal defect (AVSD)	39	31	79.49%	1	2.56%	7	17.95%	0.03	0.22
univentricular heart	28	27	96.43%	1	3.57%	0	0.00%	0.04	0.00
aortic stenosis	11	7	63.64%	3	27.27%	1	9.09%	0.30	0.10
aortic atresia	28	21	75.00%	6	21.43%	1	3.57%	0.22	0.04
coarctation of the aorta	22	16	72.73%	3	13.64%	3	13.64%	0.16	0.16
hypoplastic left heart syndrome	40	36	90.00%	1	2.50%	3	7.50%	0.03	0.08
pulmonal stenosis	20	14	70.00%	2	10.00%	4	20.00%	0.13	0.25
hypoplastic right heart syndrome	29	22	75.86%	6	20.69%	1	3.45%	0.21	0.04
transposition of the great vessels	30	22	73.33%	0	0.00%	8	26.67%	0.00	0.36
double outlet right ventricle	12	7	58.33%	4	33.33%	1	8.33%	0.36	0.09
truncus arteriosus	19	14	73.68%	4	21.05%	1	5.26%	0.22	0.06
malposition of the pulmonay arteries	6	2	33.33%	3	50.00%	1	16.67%	0.60	0.20
Fallot-tetralogy	19	13	68.42%	2	10.53%	4	21.05%	0.13	0.27
tricuspidal atresia/stenosis	7	5	71.43%	2	28.57%	0	0.00%	0.29	0.00
tricuspidal insufficiency	9	7	77.78%	2	22.22%	0	0.00%	0.22	0.00
mitral atresia/stenosis	9	7	77.78%	2	22.22%	0	0.00%	0.22	0.00
dilated right ventricle	11	9	81.82%	2	18.18%	0	0.00%	0.18	0.00
dilated right and left ventricles	5	2	40.00%	2	40.00%	1	20.00%	0.50	0.25
situs inversus	9	8	88.89%	0	0.00%	1	11.11%	0.00	0.13
dislocated heart to the right	4	3	75.00%	1	25.00%	0	0.00%	0.25	0.00
rhabdomyoma	9	8	88.89%	1	11.11%	0	0.00%	0.11	0.00
tuberous sclerosis	2	1	50.00%	1	50.00%	0	0.00%	0.50	0.00
myxoma	1	1	######	0	0.00%	0	0.00%	0.00	0.00
heart aneurysm	3	2	66.67%	1	33.33%	0	0.00%	0.33	0.00
pericardial fluid	11	10	90.91%	0	0.00%	1	9.09%	0.00	0.10
other heart anomalies	57	45	78.95%	8	14.04%	4	7.02%	0.15	0.08
congenital cystic adenomatoid malformation	16	14	87.50%	1	6.25%	1	6.25%	0.07	0.07
other lung malformations	52	22	42.31%	3	5.77%	27	51.92%	0.12	1.08
Total	**675**	**457**	**67.70%**	**96**	**14.22%**	**122**	**18.07%**	**0.17**	**0.22**

*<0.5 low ≥0.5 high ≥1 very high

Among abdominal and abdominal wall malformations, the Uncertainty factor was high in the anal atresia (0.71) and esophageal atresia (0.6) groups. Furthermore, in both anomaly groups, Difficulty factor was also very high: 2.29 in anal atresia, while 1.0 in esophageal atresia. Difficulty factor was high in case of the other abdominal malformations group as

well (0.58). Uncertainty and Difficulty factor values of abdominal and abdominal wall malformations are shown in Table 4.

Table 4 Uncertanty F(B) and difficulty factors F(N) in the detection of abdominal malformations

Type of anomaly		I.totally discovered		II. Partially discovered		III. Not detected		Uncertanty fact. F(B)*	Difficulty fact. F(N)*
	cases	n	%	n	%	n	%	II / I + II	III /I + II
esophageal atresia	20	4	20.00%	6	30.00%	10	50.00%	0.60	1.00
duodenal atresia	19	18	94.74%	0	0.00%	1	5.26%	0.00	0.06
other intestinal atresia	15	6	40.00%	3	20.00%	6	40.00%	0.33	0.67
anal atresia	23	2	8.70%	5	21.74%	16	69.57%	0.71	2.29
gastroschisis	12	12	100.00%	0	0.00%	0	0.00%	0.00	0.00
omphalocele	33	25	75.76%	3	9.09%	5	15.15%	0.11	0.18
diaphragmatic hernia	53	46	86.79%	2	3.77%	5	9.43%	0.04	0.10
abdominal cyst	8	8	100.00%	0	0.00%	0	0.00%	0.00	0.00
other	57	22	38.60%	14	24.56%	21	36.84%	0.39	0.58
total	**240**	**143**	**59.58%**	**33**	**13.75%**	**64**	**26.67%**	**0.19**	**0.36**

*<0.5 low ≥0.5 high ≥1 very high

Table 5 shows the Uncertainty and Difficulty factor values of urogenital malformations. Uncertainty factor was high in the other urogenital malformations group (0.59). We found Difficulty factor to be extremely high in the male genital anomalies group (41.00), while Difficulty factor was also high in the female genital malformations group (0.5).

The total Difficulty value was high (0.7) in case of anomalies of the limbs and bones (Table 6). Uncertainty factor was higher in case of polydactyly (0.5) and syndactyly (0.5). Difficulty factor was also very high in malformations of the fingers: 3.5 in syndactyly and 2.33 in polydactyly. It was also very high in the other malformations of the limbs group (2.0) and high in club foot (0.84).

Table 5 Uncertanty F(B) and difficulty factors F(N) in the detection of urogenital malformations

Type of anomaly		I.totally discovered		II. Partially discovered		III. Not detected		Uncertanty fact. F(B)*	Difficulty fact. F(N)*
	cases	n	%	n	%	n	%	II / I + II	III /I + II
pyelectasis	61	41	67.21%	3	4.92%	17	27.87%	0.07	0.39
other obstructive anomalies	36	32	88,.89%	3	8.33%	1	2.78%	0.09	0.03
multicystic renal dysplasia	36	29	80.56%	4	11.11%	3	8.33%	0.12	0.09
polycystic renal dysplasia	9	9	100.00%	0	0.00%	0	0.00%	0	0
renal agenesis/hpoplasia	61	32	52.46%	11	18.03%	18	29.51%	0.26	0.42
other urogenital malform.	39	11	28.21%	16	41.03%	12	30.77%	0.59	0.44
male genital	42	1	2.38%	0	0.00%	41	97.62%	0	41
female genital	24	13	54.17%	3	12.50%	8	33.33%	0.19	0.5
total	**308**	**168**	**54.55%**	**40**	**12.99%**	**100**	**32.47%**	**0.19**	**0.48**

*<0.5 low ≥0.5 high ≥1 very high

Table 6 Uncertanty F(B) and difficulty factors F(N) in the detection of anomalies of the limbs and bones

Type of anomaly		I.totally discovered		II. Partially discovered		III. Not detected		Uncertanty fact. F(B)*	Difficulty fact. F(N)*
	cases	n	%	n	%	n	%	II / I + II	III /I + II
limb reduction	17	11	64.71%	4	23.53%	2	11.76%	0.27	0.13
club foot	35	18	51.43%	1	2.86%	16	45.71%	0.05	0.84
arthrogryposis	6	5	83.33%	0	0.00%	1	16.67%	0.00	0.20
polydactyly	20	3	15.00%	3	15.00%	14	70.00%	0.50	2.33
syndactyly	9	1	11.11%	1	11.11%	7	77.78%	0.50	3.50
other limb anomalies	30	7	23.33%	3	10.00%	20	66.67%	0.30	2.00
osteogenesis imperfecta	5	4	80.00%	1	20.00%	0	0.00%	0.20	0.00
other boney anomalies	36	30	83.33%	1	2.78%	5	13.89%	0.03	0.16
total	**158**	**79**	**50.00%**	**14**	**8.86%**	**65**	**41.14%**	**0.15**	**0.70**

*<0.5 low ≥0.5 high ≥1 very high

5. Conclusions

1. In most malformation groups, the postnatally/fetopathologically detected anomalies were diagnosed with prenatal ultrasound in almost half of the cases. The results prove that ultrasound is an indispensable tool in the detection of congenital malformations, however it is unable to diagnose all the anomalies.
2. It is important to know which malformations are most commonly associated with chromosomal abnormalities. Whenever these malformations are diagnosed, it is extremely important to follow these cases closely.
3. It is also important to be aware of what anomalies are most commonly associated in multiple malformations so when one anomaly is diagnosed, it may indicate the presence of an associated but harder-to-diagnose malformation.
4. In our Clinic, birth prevalence of congenital malformations was higher than the average in the literature. This is probably due to the fact that the 1st Department of Obstetrics and Gynecology is a tercier center and therefore more congenital malformation cases are treated here than in an regular hospital.
5. It is important to know which malformations can be detected in the first trimester and we should diagnose these anomalies as early as possible.

6. Our results suggest that in cases with intrauterine retardation, thorough prenatal ultrasound assessment of the urogenital system is necessary. Furthermore, when intrauterine retardation is present at the fetus, neonatologists and pediatricians must be informed as specific postnatal examination of the newborn might be necessary.
7. The newly introduced Uncertainty F(B) and Difficulty F(N) factors fairly characterized the difficulties of the prenatal ultrasound diagnosis of congenital malformations.

6. Bibliography of the candidate`s publications

Publications closely related to the present thesis

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