

# TERATOGENIC DETERMINANTS OF FIRST- TRIMESTER EXPOSURE TO ANTIEPILEPTIC MEDICATIONS

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*Presented in part at the 31<sup>st</sup> Annual Meeting of the Society of Maternal Fetal Medicine (SMFM) San-Francisco, USA, February 7-12; 2011*

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## ABSTRACT

### Objective

To investigate the potential impact of exposure to anti epileptic medications during the first-trimester of pregnancy on major malformations.

### Study Design

A retrospective cohort study comparing all pregnancies of women with and without exposure to antiepileptic medications during pregnancy was performed. A computerized database of medications dispensed from 1998 to 2008 to all women registered in the "Clalit" health maintenance organization, was linked with computerized and non computerized databases containing maternal and infant hospitalization records from the district hospital. Exposed women were further analyzed by mono and poly- antiepileptic therapy during pregnancy. Stratified analyses, using multiple logistic regression models were performed to control for confounders.

### Results

During the study period 99,724 deliveries and 1012 pregnancy terminations occurred; of those, 421 (0.42%) were exposed to one or more antiepileptic medications during the first trimester. A higher rate of major congenital malformations was detected among women who were exposed, as compared to those unexposed to antiepileptic medications during the first trimester (10.0% vs. 7.0%; P=0.02). The association remained significant after adjusting for maternal age, ethnicity, smoking, diabetes and parity (adjusted OR= 1.50; 95% CI 1.06-2.12; p=0.02). Specifically, the risk was significant for antiepileptic anti folate drugs (n=210; adjusted OR= 1.95; 95% CI 1.25-3.03; P=0.003). Poly-antiepileptic therapy was significantly associated with major congenital malformations (26.5% vs. 5.7%, P<0.001). Using a multiple logistic regression model, controlling for ethnicity, diabetes, smoking, maternal age and parity, poly-antiepileptic therapy was an independent risk factor for major congenital malformations (adjusted OR= 7.98; 95% CI 3.4-18.7; P<0.001), while mono-therapy lost its independent association with major congenital malformations (adjusted OR= 1.23; 95% CI 0.8-1.8; P=0.28).

### Conclusion

First-trimester exposure to antiepileptic medications is an independent risk factor for major congenital malformations. The risk is significantly higher for anti folate antiepileptic drugs and for poly-antiepileptic therapy.

**Key Words:** *Antiepileptic medications; folic acid antagonists; birth defects; monotherapy; polytherapy; valproic acid; phenobarbital*

A large number of studies have been published regarding the increased rate of neonatal complications due to the teratogenicity of antiepileptic drugs. This risk for congenital malformations is approximately two to three folds higher in exposed vs. unexposed women.<sup>1</sup> Current guidelines for epilepsy treatment during pregnancy are to plan the pregnancy at disease remission and minimize dosing of antiepileptic medication during pregnancy, with 5 mg folic acid supplementation starting preconceptionally.<sup>1,2</sup>

Crawford et al documented that women who take one antiepileptic drug during pregnancy have about 3% risk for congenital malformations, slightly above the background risk, and up to 17% with polytherapy.<sup>3,4</sup> Other studies found lower rates of congenital malformations in epileptic women using antiepileptic drugs.<sup>1,2</sup> Valproate acid use during the first trimester substantially increases the risk of major congenital malformations in a dose-response manner.<sup>5-7</sup> Robert and Guibaud were the first to relate valproate and carbamazepine to neural tube defects.<sup>8</sup> A recent study found that valproate acid exposure during pregnancy is associated with an increased risk of cognitive impairment in children at 3 years of age.<sup>7</sup> Therefore, if possible, avoidance of valproate during the first trimester of pregnancy is suggested.<sup>6,7</sup> Data regarding other antiepileptic medications is less certain especially for newer antiepileptic medication.<sup>1,6</sup>

The present study was aimed to investigate determinants leading to this teratogenic risk, and specifically the effect of mono vs. poly-therapy, as well as the potential effect of anti folate seizure medications. For that end we used several computerized databases capturing large numbers of pregnancies and their outcomes.

## METHODS

### Study Population

A retrospective population-based cohort study of all pregnant women, who delivered at the Soroka Medical Center (SMC) from 1998 to 2008 was performed, using the computerized databases of the hospital. The study involved members of "Clalit" Health Services, the largest health maintenance organization in Israel. "Clalit" Health Services insures 70% of the population 15 to 49

years of age in the Beer-Sheva district in southern Israel. The district population is slightly greater than half a million inhabitants.<sup>9</sup> Soroka Medical Center (SMC) is the regional hospital, at which 98% of deliveries in the district take place.<sup>10</sup> All women 15 to 49 years of age who were registered in "Clalit" Health Services and were living in the Beer-Sheva district and who had delivered or underwent medical pregnancy terminations at SMC were included in the analyses. The study period extended from January 1, 1998, through August 31, 2008. Approximately half of the infants in the district are born to Jewish parents, and half to Bedouin Muslim parents.

### Databases

Four databases were used: the pharmaceutical database of "Clalit" Health Services in the southern district of Israel, the database of the department of obstetrics and gynecology in SMC, the demographic and hospitalization database of SMC and information about medical pregnancy terminations.

The clinical, demographic and medication data were aggregated from the computerized database of "Clalit" Health Services in the southern district of Israel and can be queried at the level of individual member. The medication data include information about the dispensed date of the medication, the Anatomical Therapeutic Chemical (ATC) classification codes of the drugs (including the commercial and generic names), the dose schedules, and the dose dispensed in terms of the defined daily dose (i.e., the assumed average maintenance dose per day).

Two computerized databases at the SMC, which draw information directly from original sources, were used. All patients' records at the hospital originate from a single database, which includes demographic information and hospitalization dates recorded at the time of the woman's admission to the hospital and at the time of the infant's birth. The database of the department of Obstetrics and Gynecology include information on maternal health status during pregnancy and delivery, maternal age, parity, gestational age at delivery, ethnic group and self-reported smoking status during pregnancy. Perinatal outcomes recorded include birth weight, Apgar score at 1 and 5 minutes, perinatal

mortality, and congenital malformations. The diagnoses are reviewed routinely by a trained medical secretary before entry into the database. The other electronic database at SMC that was used was the ICD9 database, which include demographic and medical diagnoses during hospitalization, the latter drawn directly from the medical records. Additional diagnoses related to the infant at discharge are coded and included in the infant's ICD9 record as well. All diagnoses are classified according to the International Classification of Diseases, 9<sup>th</sup> revision (ICD-9).

Supplementary data on medically induced pregnancy terminations were manually collected from a database of the committee for termination of pregnancies at our institution, encoded and linked to the SMC and "Clalit" databases by the woman's personal identification number.

The four databases (one from "Clalit" Health Services, two from SMC and one from the commission of pregnancy terminations) were linked by encoded personal identification numbers (based on numbers that are given at birth by the Interior Ministry). The study was approved by the local institutional ethics committee in accordance with the principles of the Declaration of Helsinki.

### Study Design

In this historical cohort study, we examined the association between exposure to anti epileptic medications during the first trimester and major congenital malformations. A comparison was performed between women who were exposed and unexposed to antiepileptic medications during the first trimester. Specifically we examined association between valproate and phenobarbital exposure and major malformations, as well as association between antiepileptic medications who are also anti folic acid (primidone, carbamazepine, valproate, phenobarbital, lamotrigine, phenytoin, oxcarbazepine). Another comparison was performed between mono and poly-antiepileptic therapy. Definition of exposure was dispensing of at least one of these antiepileptic medications during the first trimester of gestation.

The exposed group comprised mothers to whom antiepileptic medications were dispensed during the first trimester of pregnancy (up to 13 weeks of gestation). The first day of the last menstrual period was considered the first day of gestation. Women who were exposed to

dihydrofolate reductase inhibitors (sulfamethoxazole/trimetoprim and methotrexate) during the first trimester were excluded. Potential confounders included in the statistical analysis comprised maternal age, parity, maternal reported smoking in pregnancy, maternal diabetes mellitus and ethnicity (i.e. Jewish or Bedouin Muslims).

Major malformations were defined by the Center for Disease Control and Prevention Metropolitan Atlanta Congenital Defect Program.<sup>11,12</sup> Chromosomal malformations were excluded from the analysis. Other maternal and neonatal adverse outcomes examined were birth weight, Apgar scores less than 7 at 1 and 5 minutes, preterm delivery and perinatal mortality.

### Statistical Analysis

Statistical analysis was performed with the SPSS package version 17 (SPSS, Chicago, IL). The data processing included a number of comparisons: comparison of women who were exposed and unexposed to antiepileptic medications during the first trimester, comparison of women who were exposed to mono- antiepileptic therapy and poly-therapy to women who were not exposed and comparison of exposure to anti epileptic anti folate medications to women who were not exposed to these medications. Statistical significance was calculated using the chi square test or Fisher exact test for differences in qualitative variables and the one way Anova test for differences in continuous variables. A multivariable logistic regression model with backward elimination, was constructed, including variables with p-value <0.10 in the univariable analysis, in order to determine whether antiepileptic treatment during pregnancy is an independent significant risk factor for major malformations, low birth weight, Apgar scores less than 7 at 1 and 5 minutes, preterm delivery and perinatal mortality. Adjusted odd ratios (OR) and their 95% confidence intervals (95% CI) were computed from the logistic regression models.

## RESULTS

A total of 133,287 pregnancies took place at SMC during the study period; 100,736 (75.6%) of which to women registered at "Clalit" health maintenance organization (HMO). Of these, 421(0.4%) were exposed to at least one

antiepileptic medication during the first trimester of pregnancy. During the study period, 1012 pregnancy terminations have been performed among women who registered in "Clalit" HMO due to suspected malformation or disease in the fetus. The analysis of deliveries included 99,724

deliveries, 404 of these were exposed to at least one antiepileptic medication.

Comparison of demographic and other background characteristics of women exposed and unexposed to antiepileptic medications is presented in Table 1.

**TABLE 1** Characteristics of women exposed and unexposed to antiepileptic medications during the first trimester of pregnancy.

	Exposed to antiepileptic medications during the first trimester		Odds ratio (95%CI)	p value
	No (n)% (n=100,315)	Yes (n)% (n=421)		
Maternal Age (mean ±SD)	28.60±5.87	30.61±5.59		<0.001
Ethnic Group Bedouin Jewish (Bedouin vs. Jewish)	(63,370) 64.2 (35,933) 35.8	(194) 46.1 (227) 53.9	0.47 (0.39 – 0.57)	<0.001
Diabetes Mellitus (yes vs. no)	(6,144) 6.1	(45) 10.7	1.83 (2.50 – 1.34)	<0.001
Smoking (yes vs. no)	(2,334) 2.3	(17) 4.0	1.76 (1.08 -2.87)	0.033
Mean parity* (mean±SD)	3.72±2.66	2.59±3.78		0.635
Peripartum Fever* (yes vs. no)	(1,218) 1.2	(1) 0.2	0.20 (1.42 – 0.02)	0.104

\* Included only deliveries ( n=99,724)

Women exposed to antiepileptic drugs were more likely to be Jewish, older, tended to smoke, and had higher rates of diabetes mellitus (either gestational or pregestational) as compared to the non-exposed group.

Multiple logistic regression models were constructed in order to assess the association between antiepileptic drugs and major malformations. The models controlled for possible confounders such as maternal age, ethnicity, parity, maternal diabetes mellitus, maternal smoking and peripartum fever. The rate of major malformation in women who were exposed to antiepileptic

medications during the first trimester was higher as compared with the unexposed group (7.0% vs.10.0%). Table 2 presents the adjusted OR for major malformations and other maternal and neonatal adverse outcomes of women who were exposed to antiepileptic medications during the first trimester of pregnancy. Crude ORs were similar to the adjusted OR therefore we included only the latter. Exposure to antiepileptic medications was notes as an independent risk factor for major malformations (adjusted OR=1.50, 95% CI 1.06-2.12).

**TABLE 2** Adjusted Odds ratios for major malformations and other maternal and neonatal adverse outcomes in infants and/or fetuses that were exposed and unexposed to antiepileptic medications during the first trimester.

	Exposed to antiepileptic medications		Odds ratio	P value
	Yes (n)% (n=404)	No (n) % (n=99,724)		
Major malformations*	(42) 10.0	(7,046) 7.0	1.50 (1.06-2.02)	0.02
Preterm labor <37wk	(31) 7.7	(8,156) 8.2	0.90 (0.62-1.31)	0.60
Perinatal mortality	(5) 1.2	(1,419) 1.4	0.95 (0.39-2.32)	0.92
Low birth weight <2500gr	(39) 9.7	(10,355) 10.4	0.94 (0.67-1.31)	0.71
Very Low birth weight <1500gr	(7) 1.7	(1,664) 1.7	1.07 (0.50-2.27)	0.84
Apgar score <7 in the 1st minute†	(27) 6.8	(5,959) 6.1	1.13 (0.76-1.68)	0.51
Apgar score <7 in the 5th minute†	(5) 1.3	(1,060) 1.1	1.25 (0.51-3.04)	0.61

\* Included deliveries and pregnancies terminations (n=421 exposed; n=100,315 unexposed).

\*\* Odds ratios were adjusted for maternal age, ethnicity, parity, maternal diabetes mellitus, maternal smoking and peripartum fever.

†Data regarding 1<sup>st</sup> and 5<sup>th</sup> minute apgar scores included 97496 and 97497 deliveries, respectively.

Table 3 presents the adjusted OR for major malformations and other maternal and neonatal adverse outcomes of women who were exposed to anti epileptic anti folate medications during the first trimester of pregnancy. Exposure to anti epileptic anti folate medications during the first trimester was noted as an independent risk factor for major malformations (adjusted OR=1.95, 95% CI 1.25-3.03).

No statistical significance association was documented between exposure to antiepileptic medications and preterm labor, stillbirth and perinatal mortality, low birth weight and low

Apgar scores. Further analysis to specific malformation (CNS, cardiovascular) by the specific medication (valproate or phenobarbital) during the first trimester is shown in Table 4. No statistically significant associations were noted between these exposures and specific malformations, possibly due to inefficient statistical power. While comparing poly and mono-antiepileptic therapy (Table 5), poly-therapy, but not mono-therapy, was significant risk factor for major malformations (as compared to women who were unexposed to antiepileptic medications).

**TABLE 3** Adjusted Odds ratio for major malformations and other maternal and neonatal adverse outcomes in infants and/or fetuses that were exposed and unexposed to antiepileptic anti folate\* medications.

	Exposed to anti epileptic anti folate† during first trimester		Adjusted Odds Ratio** (95% Confidence Interval )	P Value
	No (n)% n= 99,320	Yes (n)% n=198		
Major malformations †	(7,406) 7.0	(27) 12.9	1.95 (1.30-2.93)	0.001
Preterm labor <37wk	(8,156) 8.2	(12) 6.1	0.69 (0.38-1.25)	0.228
Perinatal mortality	(1,419) 1.4	(3) 1.5	1.17 (0.37-3.67)	0.785
Low birth weight <2500gr	(10,355) 10.4	(20) 10.1	0.94 (0.59-1.50)	0.816
Very Low birth weight <1500gr	(1,664) 1.7	(3) 1.5	0.89 (0.28-2.81)	0.854
Apgar score <7 in the 1st minute††	(5,959) 6.1	(10) 5.1	0.85 (0.45-1.61)	0.628
Apgar score <7 in the 5th minute††	(1,060) 1.1	(2) 1	1.01 (0.25-4.10)	0.983

Anti epileptic anti folate medications included: carbamazepine, valproate, phenobarbital, phenytoin, lamotrigine, primidone.

\*\* Odds ratios were adjusted for maternal age, ethnicity, parity, maternal diabetes mellitus, maternal smoking and peripartum fever.

† Included deliveries and pregnancies terminations (n=210 exposed; n=100,315 unexposed)

†† Data regarding 1st and 5th minute apgar scores included 97295 and 97296 deliveries, respectively.

**TABLE 4** Adjusted odds ratios for types of major malformation in infants and/or fetuses that were exposed to valproate and Phenobarbital, compare to unexposed

	Exposure to valproate during 1 <sup>st</sup> trimester				Exposure to phenobarbital during 1 <sup>st</sup> trimester			
	No (n)% N=100315	Yes (n)% N= 31**	Adjusted* OR (95% CI)	P Value	No (n)% N=100315	Yes (n)% N=14	Adjusted* OR (95% CI)	P Value
Total major malformations	(5685) 5.7%	(5) 16.1%	2.73 (0.95-7.88)	0.06	(5685) 5.7%	(2) 14.2%	2.74 (0.61-12.28)	0.18
CNS Malformations	216 (0.2%)	(0) 0%	0	1	(216) 0.2%	(0) 0%	0	1
Cardiovascular Malformations	(2575) 2.6%	(1) 3.2%	1.47 (0.20-10.83)	0.70	(2572) 2.6%	(1) 7.1%	3.12 (0.40-23.93)	0.27

\* Odds ratios were adjusted for maternal age, ethnicity, parity, maternal diabetes mellitus, maternal smoking and peripartum fever.

\*\*Included monotherapy only.

**TABLE 5** Multiple logistic regression models for major malformations in infants and/or fetuses that were exposed to poly-therapy (model 1) and mono-therapy (model 2), compare to unexposed.

	Exposure to monotherapy during 1 <sup>st</sup> trimester (model 1)				Exposure to polytherapy during 1 <sup>st</sup> trimester (model 2)			
	No (n)% N=100104	Yes (n)% N=386	Adjusted OR (95% CI)	P Value	No (n)% N=100440	Yes (n)% N=33	Adjusted OR* (95%CI)	P Value
Total malformations in infants and / or fetuses	(5685) 5.7%	(28) 7.2	1.23 (0.83-1.83)	0.28	(5723) 5.7%	(9) 26.5	7.98 (3.40-18.71)	0.001

\* Odds ratios were adjusted for maternal age, ethnicity, mean parity, maternal diabetes mellitus, maternal smoking and peripartum fever.

## DISCUSSION

In this large cohort study, exposure to antiepileptic medications during the first trimester was identified as an independent risk factor for major malformations. Moreover, the risk for major malformations after intrauterine exposure to anti folate antiepileptic medications during the first trimester was approximately twice than among unexposed pregnancies. Poly-therapy was an independent risk factor for major malformations.

The increased risk for major malformation in infants and fetuses who were exposed to antiepileptic medications during the first trimester corroborates previous studies.<sup>1,13</sup> Our study reveals higher rates for major malformation in both exposed and unexposed to antiepileptic medications (7.0% in unexposed group and 10.0% in exposed group), compare with those from other studied.<sup>1,3</sup> These differences probably stem from our unique population, more than half of whom composed of Bedouin Arabs. Indeed, previous studies documented higher rates of congenital malformation among Bedouin Arabs which may be attributed to increased rate of consanguinity.<sup>14,15</sup> Excluding chromosomal malformations from the analysis could not eliminate the impact of consanguinity because several malformations (specifically NTD) are multifactorial and consanguinity malformations may be due to single or polygenes.<sup>16,17</sup> The definitions of major malformations in our study followed the widely used definitions of the Center

for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program.<sup>11</sup> This program has been conducting surveillance for birth defects since 1967, and its definitions have been validated in several previous studies. All infants in our system are examined after birth at the neonatology department, under the supervision of board-certified neonatologists. This may explain the higher detection rate of congenital malformations in the current report compared with other studies. The inclusion of pregnancy terminations can be another explanation for the high rate of malformations in our study. In western countries, close perinatal follow up is the standard of care, therefore prenatal detection of fetal malformations commonly lead to pregnancy termination. While other studies have been based on malformation rates only among live infants, medically induced abortion have been commonly neglected, which might cause bias in malformation rates.

Holmes et al., found higher rates of congenital malformations (6.5%) after maternal exposure to phenobarbital compared with exposure to mono-therapy with other antiepileptic medications (2.9%).<sup>18</sup> While 77 women were exposed to phenobarbital in this study, such an association could not be confirmed in other studies.<sup>1,19</sup> Likewise, we did not find significant correlation between phenobarbital exposure during the first trimester and major malformations. However, this could be the result of a relatively small number of women who were exposed to phenobarbital (n=14).

In order to properly assess the safety of phenobarbital use during pregnancy, larger cohort studies (perhaps multi-centric) are essential, especially in light of its common use in developing countries.

Valproate acid use during pregnancy was shown quite convincingly to be a risk factor of congenital malformation in a dose dependent manner.<sup>1-5</sup> Therefore, the American Academy of Neurology and the American Epilepsy have recommended avoiding its use during pregnancy.<sup>6</sup> Our relatively small number (n=31) did not allow for sufficient statistical power to show a significant and independent association, although valproate acid did approach statistical significance.

Kajaa et al. examined 740 epileptic women who were treated with antiepileptic medications during pregnancy.<sup>20</sup> A rate of 3.1% for congenital malformation after mono-therapy exposure was found, 5.8% for the use of two antiepileptic medications and 8.3% for the use of three or more antiepileptic medications during pregnancy. Morrow et al examined 3,186 who were treated with antiepileptic medications during pregnancy and found 3.7% rate for congenital malformations after mono-therapy and 6% after poly-therapy.<sup>21</sup> Canger et al were among the few that did not found higher risk for congenital malformation after exposure to two or more antiepileptic medications or more during pregnancy.<sup>22</sup> Our results support the strong association between poly-therapy and major congenital malformations.

Importantly, in this cohort study exposure to antiepileptic medications during pregnancy was not found as independent risk factor for other maternal and neonatal adverse outcomes such as preterm labor, perinatal mortality and stillbirth, low birth weight and low Apgar score. Several previous studies have found an increased risk for maternal and neonatal complications in epileptic women who were exposed to antiepileptic medications during pregnancy.<sup>2,23</sup> A possible explanation for these differences may be selection bias of women with severe disease treated with antiepileptic medications, as in the study of Sawhney and his colleague, that found an association to low birth weight only in women with epilepsy that had seizure during pregnancy.<sup>24</sup> As most previous studies, we did not find high risk for perinatal mortality and stillbirth. Nevertheless, the rate of perinatal mortality and

stillbirth in western world countries is small and very large cohort studies are needed in order to obtain a sample with an appropriate power. Our study has several advantages. First we included a large number of women who were exposed to several types of antiepileptic medications during the first trimester, and from different ethnic groups. Second, this study included information about medical pregnancy terminations. Nevertheless, an important limitation of our study is lack of data regarding adherence. Some women may have been aware of the teratogenicity of antiepileptic medications during pregnancy, thus decided not to take the medications during pregnancy. In a previous study conducted by our group, we examined the compliance to medications by other studies which have been conducted on the same populations<sup>25</sup> finding that rates of medication compliance were >90% in two subgroups of our cohort (women with deep vein thrombosis treated with enoxaparin<sup>26</sup> and women with Familial Mediterranean Fever treated with colchicines<sup>27</sup>). It is reasonable that these high adherence rates can be generalized to women treated with antiepileptic medications. Similar to our data, previous studies have shown that computerized pharmacy records may be an accurate source of medication data and have high rates of concordance with self reports of medications used by patients in general and by pregnant women in particular.<sup>28,29</sup>

It may be that apart from the antiepileptic medications, epilepsy itself or severe seizures with consciousness loss can also harm the fetus during pregnancy. Several studies were conducted in order to determine whether the disease or drug therapy is the main cause of harm to the fetus. Meadow was among the first to suggest that the risk for congenital malformations was mainly due to medications treatment and not due to the disease per-se.<sup>30</sup> Holmes et al found no increased risk of congenital malformations among women with a history of seizures without drug treatment and control groups.<sup>31</sup> Accordingly, it is acceptable that the risk for congenital malformations is mainly due to medications exposure during pregnancy.<sup>2</sup>

The mechanism of antiepileptic medications teratogenicity is not entirely clear however one hypothesis is anti folate effect.<sup>31</sup> The anti folate effect is attributed to carbamazepine, valproate,



phenobarbital, lamotrigine, phenytoin, oxacarbazepine and primidone.<sup>32,33</sup> Dansky et al., found a correlation between low rate of folic acid in red blood cells and antiepileptic medications exposure.<sup>33</sup> Recently, high risk for major malformations after folic acid antagonists including some antiepileptic medications was documented.<sup>31</sup> Indeed, our results support the hypothesis of anti folate effect of antiepileptic medications.

In conclusion, first-trimester exposure to antiepileptic medications is an independent risk factor for major congenital malformations, while the risk is significantly higher for antiepileptic anti folate drugs and for poly-therapy. Thus, poly-therapy and valproate should be avoided if possible. Five mg folic acid supplements should begin preconceptionally, and close perinatal surveillance should be performed in order to detect fetal malformations as soon as possible.

#### **Acknowledgements/ Funding**

We would like to thank the Computer Units of Clalit Southern District and Soroka Medical Center.

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CPNDS Symposium available online:  
Vol 18(1):e76-e175

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