The Effect of Chemical Compounds from Cigarettes Smoke on First Trimester Biochemical Markers

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Previous studies showed that certain behavioral and physical parameters influence the concentration of first trimester biochemical markers. The scope of the present article was to study the relationship between smoking and first trimester screening biochemical markers and the capability of the software to counterbalance this influence. Concentrations of pregnancy-associated protein A (PAPP-A) and free β chorionic gonadotropin hormone (free β hCG) were measured in sera of 1554 first trimester pregnant women, 1349 of which were non-smokers and 205 were smokers. First trimester PAPP-A values are lower in smoking compared to non-smoking pregnant women (0.94±0.04 vs. 1.09±0.02, p=0.0004), since smoking seems not to influence free β hCG concentration (1.11±0.07 vs. 1.03±0.02, ns). The software used by us corrected successfully the effect of chemical compounds from cigarette smoke on PAPP-A values.

Key words: PAPP-A, free β hCG, first trimester biochemical markers, aneuploidies, smoking, software correction

Cigarette smoking releases thousands of chemicals [1]. Most of them are inhaled and diffused in lungs via pulmonary alveoli in blood. Some of smoke compounds are made responsible for certain diseases: nicotine dependence, cancer, chronic lung diseases, etc [2]. Chemicals from cigarette smoke also determine changes of homeostasis and of the value of serological and biochemical parameters [3]. Obviously, such an effect is also observed in pregnant women who smoke [4,5]. Since some of blood biochemical parameters influenced by inhalation of chemical compounds released by smoking are used to assess the risk of fetal aneuploidy, it is imperative to quantify the degree of alteration and to develop algorithms to counterbalance this effect [6-9].

Nowadays the most recommended first trimester aneuploidies screening protocol is the combined test [10]. The combined screening test protocol was developed by Fetal Medicine Foundation and relies on the determination of certain ultrasound and biochemical markers [10]. The ultrasound markers included in the risk evaluation algorithm are the crown-rump-length (CRL), nuchal translucency thickness (NT), nasal bone, ductus venosus Doppler, tricuspid Doppler, and fetal heart rate. To get a complete assessment of aneuploidies risk the ultrasound markers mentioned above are combined with two biochemical markers: free-β -hCG and PAPP-A [10].

Risk calculation formula converts the absolute value of a biochemical marker into a value named multiple of median or MoM. MoM is a unit which appreciates the deviation of the value of a parameter from the median value of the same parameter in the population of pregnant women who carry a healthy fetus. The deviation is used in an algorithm to assess the relative risk for aneuploidies. Since the MoM value directly contributes to the evaluation of the risk, any alteration of values by behavioral, environmental or morphologic factors could negatively influence the accuracy of the screening test [6-9]. As a result, mathematical strategies were developed to correct the influence of these disturbing factors. When the correction for presence of the disturbing factor is included in the calculation of the deviation from the median, we obtain a corrected value of Multiple of Median or MoMc.

Previous research identified cigarette smoke among factors that influence the value of first trimester biochemical markers [9]. Since a significant percent of pregnant women smoke, in our article we aim to evaluate the influence of smoking on first trimester biochemical markers and the capability of our software to correct this influence [1,5,9].

Experimental part
Patients and sera

Pregnant women (n=1554) were screened for aneuploidies based on a combined first trimester screening program. All pregnant women benefit from the measurement of first trimester ultrasound markers (crown-rump length and nuchal translucency) and biochemical markers (PAPP-A, free β hCG) between 11+4 and 13+6 weeks of pregnancy (wop). Only Caucasian pregnant women who spontaneously conceived, without diabetes

and with singleton pregnancies, were included in our study. Pregnant women were interrogated about the date of the last menstrual period, mode of conceiving, smoking behavior, presence of diabetes, and weight at the time of biochemical screening. Gestational age was determined according to Kalish, Chervenak et al. on basis of CRL values [11]. From 1554 pregnant women 1349 were non-smokers and 205 were smokers.

First trimester biochemical markers measurement
PAPP-A and free β hCG biochemical markers were measured by the chemiluminescence method, using an ImmuliteOne Machine (DPC, Diagnostic Products Corporation, Los Angeles, USA) and commercially available kits (Siemens Healthcare Diagnostics Products Ltd., Llanberis, Gwynedd, LL55 4EL, UK). Values were expressed in multiple of medians (MoM), corrected multiple of medians (MoMc), calculated according to PRISCA software, Version 4 (Typolog Software, Tomesch, Germany). Data were stored according to a protocol presented elsewhere [12, 13].

NT and CRL measurement
Crown-rump length and nuchal translucency were measured according the fetal medicine foundation (FMF) guidelines.

Ethical issues
The research meets the conditions of the ethical guidelines and legal requirements and was approved by the Committee of the University of Medicine and Pharmacy Timisoara. Informed consent was obtained from every patient.

Statistical analysis
Data are expressed in median+/- Standard error of mean (SEM). GraphPad InStat software, San Diego, California, USA and SPSS, IBM Inc. were used for statistical analysis. Mann-Whitney sum of ranks test was used to compare series of values.

Results and discussions
With the increasing age of pregnant women in the last decades, the importance of risk assessment in pregnancies is becoming more and more obvious. Nowadays advances in technology give us the possibility to evaluate from the first trimester the risk of fetal aneuplodies [14,15], of preterm birth [16] or pregnancy-induced hypertension [17]. Also by increasing access to laboratory methods, most pregnant women benefit from investigations for infectious diseases [18,19] and endocrinopathies [20]. In this framework, our study is intended as a contribution to ensuring more safety during pregnancy.

Comparison of demographic data of pregnant women: non-smokers vs smokers
At the time of screening the age of non-smoking pregnant women was higher than of those who smoke (28.74 years vs. 27.43 years), the gestational age was similar (87.00 days vs. 87.00 days), and no difference related to weight between the two groups was found (61.00 kg vs. 60.00 kg) (table 1).

First trimester biochemical markers (PAPP-A and free β hCG) in non-smoker vs. smoker pregnant women
Free βhCG concentration showed similar values in the two groups whereas PAPP-A values were lower in smoker than in non-smoker pregnant women. The difference reached an extremely significant threshold (table 2).

Software counterbalance of smoking influence on first trimester biochemical markers values
The influence of smoking on first trimester biochemical markers values was corrected by the software. No difference was found between the corrected multiple of median (MoMc) values in sera of non-smoking and smoking pregnant women (table 3).
The above results are, to the best of our knowledge, the first ones that bring detailed data about the smoking behavior of pregnant women in our country and analyze the effect of smoking on first trimester biochemical markers. The percentage of smoking pregnant women was similar to other countries [1,5,9].
Since previous similar studies analyzed data obtained in systems provided by others, this research is the first one which analyzed data obtained in the engine used by us [8,9].
Interestingly, our results confirm the data which showed that PAPP-A values are lower in pregnant women which smoke. The software successfully corrects this effect.

	non-smoker	smoker	significance
Age (years)	28.74±0.13	27.43±0.34	0.004
Gestational age (days)	87.00±0.13	87.00±0.32	0.41 (ns)
Weight (kg)	61.00±0.34	60.00±0.88	0.53 (ns)
Number of pregnant women	1349	205	

Table 1
DEMOGRAPHIC FEATURES OF PREGNANT WOMEN INCLUDED IN THE STUDY

Data are expressed in median ± SEM

	non-smoker	smoker	p-value
Free ß hCG	1.03±0.02	1.11±0.07	0.46 (NS)
PAPP-A	1.09±0.02	0.94±0.04	0.0004

Table 2
COMPARISON OF MoM VALUES OF FIRST TRIMESTER BIOCHEMICAL MARKERS IN NON-SMOKER (n=1349) VERSUS SMOKER PREGNANT WOMEN (n=205)

Values are expressed in multiple of medians (MoM)

	non-smoker	smoker	p-value
Free ß hCG	1.05±0.02	1.10±0.07	0.52 (NS)
PAPP-A	1.08±0.02	1.09±0.04	0.87 (NS)

Tabel 3
STATISTICAL EVALUATION OF SECOND TRIMESTER BIOCHEMICAL MARKERS VALUES CORRECTED FOR SMOKING IN NON-SMOKER (n=1089) VERSUS SMOKER PREGNANT WOMEN (n=153)

Values are expresses in corrected multiple of medians (MoMc).

We did not have the possibility to analyze whether this effect is dependent on gestational age or on the number of cigarettes smoked daily [9]. This is to be done in our further studies which will analyze and compare our results with data obtained in systems provided by others.

Conclusions

Our research confirms for the first time in a study performed on our population that smoking influences the first trimester PAPP-A concentration and shows that the software used by us is able to correct this influence.

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