# Influence of Weight of Pregnant Women on First Trimester Biochemical Markers Values

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*Values of first trimester biochemical markers (PAPP-A and free b-hCG) concentration are included in aneuploidies risk evaluation algorithm. Since both markers are produced by the fetus and placenta their concentration depends on the volume in which they are dissolved, respectively the weight of the pregnant women. Our study aimed to analyze the influence of maternal weight on first trimester biochemical markers concentration and the ability of the risk calculation software to correct this influence. Pregnancy-associated protein A (PAPP-A) and free ß chorionic gonadotropin hormone (free ß hCG) first trimester sera concentration respectively weight were measured in 1629 pregnant women. First trimester PAPP-A and free beta hCG concentrations inverse correlate with weight of pregnant women rho=-0.33, p<0.0001, respectively rho=-0.18, p<0.0001. Weight of pregnant women inversely correlates with multiple of median (MoM) values of first trimester markers too: rho=-0.38, p<0.0001 (PAPP-A), respectively rho=-0.17, p<0.0001 (free-b-hCG). The software counterbalances the influence of weight on biochemical markers values. PAPP-A corrected MoM (MoMc) values don't inversely correlate with the weight (rho=-0.03, p=0.12), whereas free ß hCG MoMc values showed an extremely weak inverse correlation (rho=-0.08, p=0.0008). The software counterbalances the influence of weight on PAPP-A values, whereas an extremely weak but insignificant inverse correlation between weight and free-beta hCG values persists after correction.*

*Keywords: PAPP-A, free β hCG, first trimester biochemical markers, aneuploidies, weight, software correction*

The biochemical markers included in the first trimester screening algorithm are free beta human chorionic gonadotropin hormone (free-β-hCG) and pregnancy associated plasma protein A (PAPP-A) [1]. Based on the age of pregnant women, the values of first trimester biochemical and ultrasound markers (nuchal translucency, presence of nasal bone, Doppler evaluation) a risk of fetal aneuploidies could be calculated for each pregnancy [2].

Free-β-hCG is produced mainly by trophoblast cells [3]. Sometimes tumor cells could also produce hCG [3]. Free-β-hCG is a hyperglycosylated form of hCG [3]. Palomaki described well why in pregnancies that carry Down syndrome fetuses the delay in differentiation of trophoblastic cells determines an increase of hCG accumulation [4]. Thus, hCG values are increased in serum of these pregnant women and are used to screen for pregnancies with Down Syndrome [4].

PAPP-A is a protein produced by placenta which increases about 150 times in pregnancy [3]. In serum PAPP-A is present as a 500 kDa heterotertameric 2:2 complex with the proform of eosinophil major basic protein (proMBP) [5]. PAPP-A have an important role in placental and embryo development [6]. Low PAPP-A values are present in pregnacies that carry Down syndrome fetuses.

Previous research defines median values of first trimester biochemical markers concentration for each gestational age in pregnant women that carry healthy fetuses. For a certain pregnant woman the deviation of concentration of a biochemical marker from the attempted median is quantified as a multiple of median (MoM). Studies showed that concentrations of biochemical markers are influenced not only by the status of the fetus but by some features of the pregnant women too. Studies analyzed physical and behavioral features of pregnant women that influence the concentrations of biochemical markers: smoking status [1,7,8], weight, rhesus group and localization of placental insertion [9], ethnicity or mode of conceiving. In order to counterbalance the influence of the factors described above on concentrations of biochemical markers values, compensatory mathematical algorithms were developed. The corrected MoM (MoMc) values are obtained after compensation of the influence of other factors than the fetus on biochemical markers concentrations.

In our study we aim to analyze the influence of weight of pregnant women on first trimester biochemical markers and to prove the efficiency of risk calculation software in proper counterbalancing this effect.

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## Experimental part

*Patients and sera*

1629 first trimester pregnant women benefited from a first trimester aneuploidies screening. First trimester ultrasound markers (crown-rump length and nuchal translucency) and biochemical markers (PAPP-A, free β hCG) were measured between 11+4 and 13+6 weeks of pregnancy (wop) in all pregnant women. In our study were included only pregnant women of Caucasian ethnicity who conceived spontaneously, without diabetes, and with singleton pregnancies. Last menstrual period, mode of conceiving, smoking behavior, presence of diabetes, and weight at the time of biochemical screening were noted as described before [10,11]. A protocol according to Kalish, Chervenak et al. was used to calculate the pregnancy age on basis of CRL values [12].

*Measurement of values of first trimester biochemical markers*

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), and calculated according to PRISCA software, Version 4 (Typolog Software, Tomesch, Germany).

*Establishment of gestational age*

Crown-rump length was used to determine gestational age [12].

*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

Accurate evaluation of aneuploidy risk by combined first trimester screening test implies the elimination of the effect of disturbing factors (smoking, ethnicity, method of conception, presence of diabetes or the weight of the pregnant woman) on biochemical markers concentration [1,7,8]. We herein analyze the effect of weight of pregnant women on PAPP-A and free β hCG seric concentration, and the availability of the risk calculation software to correct this effect.

*Demographic and serological features of pregnant women in the study*

The first trimester aneuploidy screening was performed at gestational age of 87.00±0.12 days respectively at a crown-rump length (CRL) of 59.49±0.24 mm. The age of pregnant women was 28.72±0.12 years and the weight 61±0.31 kg (table 1). The absolute value, multiple of median (MoM) and corrected multiple of median (MoMc) values were 37.4±0.83, 1.05±0.2 and 1.06±0.02 for PAPP-A respectively 3.3±0.06, 1.07±0.01 and 1.08±0.01 for free β hCG (table 2).

**Table 1**

DEMOGRAPHIC FEATURES OF PREGNANT WOMEN

| Demographic features | Median±SEM |
|---|---|
| Age (years) | 28.72±0.12 |
| Gestational age (days) | 87.00±0.12 |
| Weight (kg) | 61±0.31 |
| CRL (mm) | 59.49±0.24 |
| Number of pregnant women | 1629 |

*Data are expressed in median ± SEM*

**Table 2**

SEROLOGICAL FEATURES OF PREGNANT WOMEN

| Serological parameter | PAPP-A | free ß hCG |
|---|---|---|
| Absolute value | 37.4±0.83 | 3.3±0.06 |
| MoM | 1.05±0.2 | 1.07±0.02 |
| MoMc | 1.06±0.02 | 1.08±0.01 |
| Number of pregnant women | 1629 | 1629 |

*Data are expressed in median ± SEM*

*Inverse correlation between the weight of pregnant women (Kg) and PAPP-A concentration*

An extremely significant inverse correlation was found between the weight of pregnant women and absolute PAPP-A values and MoM PAPP-A values whereas no correlation was found with corrected MoM values (table 3).

**Table 3**

CORRELATION BETWEEN THE WEIGHT OF PREGNANT WOMEN (Kg) AND PAPP-A VALUES

| weight vs. PAPP-A | absolute value | Multiple of Median (MoM) | Multiple of Median corrected (MoMc) |
|---|---|---|---|
| Rho | - 0.3325 | - 0.3886 | - 0.0385 |
| p- value | < 0.0001 | < 0.0001 | 0.12 (NS) |

| weight vs. f-bhCG | absolute value | Multiple of Median (MoM) | Multiple of Median corrected (MoMc) |
|---|---|---|---|
| Rho | - 0.1760 | - 0.1707 | - 0.0827 |
| p- value | < 0.0001 | < 0.0001 | 0.0008 |

**Table 4**

CORRELATION BETWEEN THE WEIGHT OF PREGNANT WOMEN (Kg) AND FREE β hCG VALUES

*Inverse correlation between the weight of pregnant women and free β hCG values*

An inverse correlation was found between the weight of pregnant women and absolute respectively MoM *free β hCG* values. We found an inverse correlation between weight of pregnant women and *free β hCG* MoMc, although it was weak (table 4).

Our study analyzed for the first time in our country the effect of the weight of pregnant women on sera concentration of first trimester biochemical markers and the capability of a software dedicated to first trimester aneuploidy risk evaluation to counterbalance this influence.

The most worldwide-promoted fetal aneuploidies screening program is the first trimester combined test [1,2]. The combined screening test protocol was developed by Fetal Medicine Foundation and relies on the determination of the described ultrasound and biochemical markers [2].

Since the precision of risk evaluation depends on accuracy of corrected MoM values calculation, it is mandatory to appreciate the capability of the risk evaluation software to counterbalance the effect of factors other than the fetus which influence the MoMs [1,7-9]. We found an inverse correlation between weight and biochemical markers concentration. We described the exact value of the inverse correlation and showed that the inverse correlation between weight and PAPP-A was stronger than the inverse correlation between weight and free β hCG. Then we tested how well the software that we used to calculate the risk of aneuploidies counteracts the effect of weight on first trimester markers concentrations. In this respect we analyzed the correlation between weight and PAPP-A/free β hCG corrected MoM values. Since no inverse correlation was found with PAPP-A MoMc, a weak inverse correlation between weight and free β hCG MoMc values was still present. These results showed that the software realize an excellent compensation of influence of weight on PAAP-A MoMc values.

In our paper we haven't analyzed the simultaneous influence of both smoking status and weight on first trimester biochemical markers or the influence of one of these parameters in pregnant women stratified on groups according to the smoking status, weight or gestational age at the time of screening. These will be the objectives of next studies. Moreover, further studies should analyze the consequences of correlation between weight and PAPP-A MoMc values on the aneuploidies risk evaluation and a comparison with the performance of other software providers.

## Conclusions

The weight of pregnant women inversely correlates with first trimester biochemical markers values. The software used for aneuplodies risk evaluation corrects the influence of weight of pregnant women on PAPP-A values but a minute influence on free β hCG values is still present. Since the correlation between corrected MoM free β hCG values and weight is extremely weak, it could probably be neglected. Further studies should analyse this effect.

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