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# Increased Rate of Chromosomal Abnormalities in PHO Clinical Hospital Bitola in the Period 2018-2020

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## Abstract

**Background:** Down's syndrome and Edwards' syndrome are the most common chromosomal abnormalities. Prenatal screening is a very important diagnostic tool for the detection of chromosomal abnormalities which is done in the first trimester of the pregnancy between 11 and 14 weeks of gestation.

**Methods**: In this study we use dual marker test, which is a first-trimester screening test. The markers for this test are PAPP-A (pregnancy-associated plasma protein-A) and freeβ-hCG (beta human chorionic gonadotropin).

**Results:** Our study includes 1733 women in a period of three consecutive years (2018-2000). 1597 (92%) of them were negative on the screening, indicating low risk for chromosomal abnormalities, and 136 (8%) women tested positive, indicating increased risk. We concluded that pregnancies with an increased risk of chromosomal abnormality have strong correlation with advanced maternal age. Also, β-hCG is higher in pregnancies with risk, and PAPP-A is lower in pregnancies with increased risk for chromosomal abnormality. Also, we conclude that rate of pregnancies with increased risk for chromosomal abnormality increased from 5% in 2018 to 11% in 2020 year.

**Conclusion:** The incidence of chromosomal abnormalities in pregnant women has been growing in the last three years, and these worrying findings impose the need to find out the cause of this phenomenon. The dual marker test is a very important tool for practitioners practitioner, because fetal chromosomal abnormalities can be diagnosed early in gestation and provide enough time for a confirmative test and if the risk of pregnancy is confirmed, it can be terminated in time.

***Keywords:*** *PRISCA; PAPP-A; Free B-Hcg; Chromosomal Abnormalities*

## Introduction

Down's and Edward's syndromes are the most common chromosomal abnormalities, with neonatal incidences of 1/800-1/600 [1] and 1/2600–1/2500, respectively [2].

Chromosome abnormalities are present in 15% of the congenital anomalies in pregnancy in Europe, and they are associated with 25% of perinatal deaths due to congenital anomalies in all pregnancies [3].

Prenatal screening for Down's and Edward's syndromes are a very important diagnostictool for the detection of chromosomal abnormalities done in the first trimester of pregnancy, between 11 and 14 weeks of gestation.

Prenatal screening includes ultrasound measurementof nuchal translucency (NT) and the determination of Fetal-maternalserum biomarkers: pregnancy-associated plasma protein-A (PAPP-A) and free beta human chorionic gonadotropin (free β-hCG) [4-7].

For risk assessment, from chromosomal abnormalities, additional factors included in the PRISKA method used for risk assessment of pregnant women are:maternal age, racial origin, weight, diabetic status, smoking and method of conception. The risk of Down's syndrome is determined i.e. calculated by a combination of software processing of the maternal characteristics, biochemical and sonographic markers [8].

## Methods

In our study we evaluate the data of 1,733 pregnant women who were admitted in the PHO Clinical Hospital in Bitola, North Macedonia and underwent first-trimester screening test in the laboratory of Medical Biochemistry in the period of 2018 and 2020. Their gestational ages were 8 - 13 weeks and they were living in Bitola and environment.

We use the dual marker test (DMT), which is a first-trimester screening test that is performed between 8-14 weeks of gestation (9).The markers for this test are PAPP-A and free β-hCG [10].

Statistical risk is calculated using a computerized program with PRISCA 5 software. It calculates the risk for trisomy 21 andtrisomy 18.

We determined serum levels of free β-hCG and PAPP-A by IMMULITE® 2000hpi device (Diagnostic Products Corporation, Los Angeles, CA, USA) which run with chemiluminescence method and belongs to BIO-DPC company. Gestational age defined according to crown-rump length (CRL) determined ultrasonographically. An ultrasound system (VolusonE8, GE) was used for prenatal diagnosis. First trimester screening test cut-off values were accepted as 1/250 for Down's syndrome and Edwards' syndrome.

SPSS 17.0 software (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.) was used for statistical analysis.

## Results

Of these 1733 women, 1597women (92%) had negative screening results, indicating low risk for chromosomal abnormalities and 136 (8%) women tested positive, indicating increased risk.

Demographic values of pregnant women (n = 502) included in this study in 2018 year are shown in table 1.

| 2018 year N=502 | Minimum values in pregnancies with low risk N=476 | Minimum values in pregnancies with high risk N=26 | Maximum values in pregnancies with low risk N=476 | Maximum values in pregnancies with high N=26 | Mean values in pregnancies with low risk N=476 | Mean values in pregnancies with high N=26 | Stadndard Deviation values in pregnancies with low risk N=476 | Stadndard Deviation values in pregnancies with high N=26 |
|---|---|---|---|---|---|---|---|---|
| Age | 16 | 23 | 43 | 38 | 29 | 31.9 | 7.7 | 10.7 |
| Gestational week | 8 | 11 | 13 | 13 | 11 | 11.8 | 0.7 | 0.7 |
| Body weight (kg) | 41 | 48 | 121 | 101 | 66 | 70 | 4.94 | 10.9 |
| CRL | 37.7 | 41.7 | 83.5 | 75.7 | 60 | 60.7 | 4.66 | 10.53 |
| NT | 0.5 | 0.5 | 3.1 | 6 | 1.34 | 1.61 | 0.49 | 0.14 |
| Free β-hCG | 6.1 | 6.2 | 186 | 467 | 40 | 65.58 | 41.6 | 11.1 |
| PAPP-A | 0.63 | 0.49 | 18.7 | 5.26 | 3.94 | 1.77↓ | 5.43 | 1.99 |

***Table 1:*** *Demographic characteristics of pregnancies in 2018 year.*

In the table 1 is shown that the median maternal age in women with normal pregnancies is lower compared to pregnancies with increased risk for chromosomal abnormality, 29 vs. 31.9. Also, we have noted that NT is increased from 1,34 for normal pregnancies to 1,61 in pregnancies with risk and free β-hCG is the same increased from 40 in normal pregnancies to 65.5 in pregnancies with increased risk is.

PAPP-A have lower values from 3,94 in normal pregnancies to 1.77 in pregnancies with increased risk for chromosomal abnormality.

From the table 2 we can conclude that the median maternal age in women with normal pregnancy is lower compared to pregnancies with increased risk for chromosomal abnormality, 30.7 vs. 34. Also, we had noted that CRL and Free β-hCGinpregnancies with increased risk is increased, for CRL 52.5 for normal pregnancies to 61 in pregnancies with risk, and for free β-hCG is 78,4 in normal pregnancies to 99.1 in pregnancies with increased risk for chromosomal abnormality.

| 2019 year N= 666 | Minimum values in pregnancies with low risk N=618 | Minimum values in pregnancies with high N=48 | Maximum value sin pregnancies with low risk N=618 | Maximum values in pregnancies with high N=48 | Mean values in pregnancies with low risk N=618 | Mean values in pregnancies with high N=48 | Stadndard Deviation values in pregnancies with low risk N=618 | Stadndard Deviation values in pregnancies with high N=48 |
|---|---|---|---|---|---|---|---|---|
| Age | 13 | 22 | 39 | 43 | 30.7 | 34 | 10.8 | 13.7 |
| Gestational week | 10 | 10 | 13 | 13 | 11 | 12 | 0.7 | 0.7 |
| Body weight (kg) | 37 | 42 | 130 | 110 | 81 | 70 | 19 | 23.3 |
| CRL | 37 | 41 | 83.4 | 77 | 52.5 | 61 | 2.12 | 11.2 |
| NT | 0.5 | 0.8 | 3 | 5.6 | 1.3 | 1.45 | 0.28 | 0.14 |
| Free β-hCG | 6.1 | 6.89 | 273 | 502 | 78.4 | 99.1 | 94.1 | 127.3 |
| PAPP-A | 0.52 | 0.44 | 26.1 | 6 | 3.06 | 1.89 | 2.88 | 3.5 |

***Table 2:*** *Demographic characteristics of pregnancies in 2019 year.*

PAPP-Ar results have shown lower values in pregnancies with increased risk for chromosomal abnormality from 3.06 in normal pregnancies to 1.89 in pregnancy with increased risk.

In the table 3 it can beobserved that the median maternal age in women with normal pregnancy is lower, compared to pregnancies with increased risk for chromosomal abnormality, 28 vs. 34. We have notedincreasedfree β-hCGinpregnancies with increased risk from 49,4 to 99,1, and decreased PAPP-Ain pregnancies with increased risk for chromosomal abnormality from 4 in normal pregnancies, to 1,89 in pregnancies with risk.

| 2020 year N=565 | Minimum values in pregnancies with low risk N=503 | Minimum values in pregnancies with high N=62 | Maximum values in pregnancies with low risk N=503 | Maximum values in pregnancies with high N=62 | Mean values in pregnancies with low risk N=503 | Mean values in pregnancies with high N=62 | Stadndard Deviation values in pregnancies with low risk N=503 | Stadndard Deviation values in pregnancies with high N=62 |
|---|---|---|---|---|---|---|---|---|
| Age | 16 | 24 | 42 | 43 | 28 | 34 | 0.37 | 13.7 |
| Gestational week | 10 | 11 | 13 | 13 | 12 | 12 | 0.7 | 0.7 |
| Body weight (kg) | 41 | 45 | 130 | 118 | 67.8 | 68 | 16.9 | 9.88 |
| CRL | 37.8 | 41 | 82.3 | 77 | 62 | 61 | 7.7 | 11.2 |
| NT | 0.53 | 0.8 | 2.2 | 5.6 | 1.35 | 1.45 | 0.04 | 0.14 |
| Free β-hCG | 7.8 | 6.89 | 245 | 502 | 49.4 | 99.1 | 78.27 | 127.3 |
| PAPP-A | 0.63 | 0.44 | 22.7 | 6 | 4 | 1.89 | 10.2 | 3.5 |

***Table 3:*** *Demographic characteristics of pregnancies in 2020 year.*

Analyzing these 3 years, from 2018 to 2020, we concluded that the pregnancies with increased risk of chromosomal abnormality havestrong correlation with advanced maternalage. Also, free β-hCG is higher in pregnancies with risk, and PAPP-A is lower in pregnancies with increased risk for chromosomal abnormality.

Table 4 is showing that rate of pregnancies with increased risk for chromosomal abnormality increased from 5% in 2018 to 11% in 2020 year.

| Year | 2018 year | 2019 year | 2020 year |
|---|---|---|---|
| Number of pregnancies with increased risk | 26 | 48 | 62 |
| Percent of screen positive indicating increased risk | 5% | 7% | 11% |
| Biochemical risk for Tr.21 | 20 | 44 | 60 |
| Scan+Biochemical risk for Tr.21 | 8 | 7 | 10 |
| Biochemical risk for Tr.18 | 6 | 10 | 5 |
| Scan+Biochemical risk for Tr.18 | / | 4 | 1 |
| Biochemical risk for Tr.21&18 | / | 7 | 2 |

***Table 4:*** *Present risk of chromosomal abnormality in 2018-2020 year.*

Over the past few years, we have witnessed an upward, negative trend in the incidence of fetal chromosomal abnormalities in our Hospital. This has a strong correlation with advanced maternal age. The results of other studies analyzing the same prenatal markers in pregnant women are in correlation with our study. According to EUROCAT (European Surveillance of Congenital Anomalies), the proportion of mothers aged 35 years or older, increased from 13% in 1990 to 19% in 2009, and accompanied an increase of trisomy-affected pregnancies [11]. In Western Australia, the rate of Down's syndrome pregnancies increased from 1.1 to 2.9 per 1000 births; births for women aged 35+ years have increased from 8% to 20% during 1980 - 2013 [12].

In our study, women of advanced age were at higher risk of chromosomal abnormalities. Previous studies have shown that women of advanced maternal age have a higher incidence of Trisomy 21, although the precise mechanisms underlying these observations remain unclear [13,14].

In the last two decades, there have been numerous reports about the detection rate for different methods of screening for trisomy 21. Detection rate of the risk of maternal age and fetal NT is 75 - 80%, while the risk for age and biochemical screening of PAPP-A and free beta HCG is 70%. The combination of age-related risk markers NT, PAPP-A and free beta HCG increases the detection of trisomy 21 to 85 - 95% [15,16].

The ability to achieve a reliable and precise measurement of NT is dependent on the appropriate training of sonographers [17].

First-trimester screening protocols include maternal serum analytes and ultrasonographic examination. Free β-hCG and PAPP-A are the most important serum analytes for first-trimester screening [18].

PAPP-A is decreased in Down's syndrome pregnancies, and free β-hCG is elevated. Studies on higher risk pregnancies showed an increased risk of aneuploidy associated with increased NT. NT is a sonolucent fluid filled space beneath the skin at the back of the neck. It can be measured between 11 and 14 gestational weeks by transabdominal ultrasonography [19].

NT was the best single ultrasonographical marker, with a detection rate more than 70%. Fetuses at risk for neural tube defects or fetal chromosome abnormalities, as well as women at risk for third-trimester obstetrical complications, can be defined by prenatal screening tests. Maternal serum screening has the benefit of earlier diagnosis, decreasing fetal mortality, morbidity, and helping couples to decide about appropriate delivery strategies [20].

Couples with positive screening test results should be informed about Down's syndrome and complications of invasive procedures for specific diagnosis [21].

Ardawi., *et al.* examined the distribution of MoM values of fetal NT, free β-hCG and PAPP-A in Saudi singleton pregnancies, and they found that the maternal body weight, smoking, twin pregnancy and ethnicity are important factors for first-trimester screening test results [22].

Different study groups have examined whether there is a relationship between abnormal serum levels of free β-hCG, PAPPA in the first-trimester and subsequent pregnancy complications like fetal growth retardation or preterm labour and they found conflicting results [23].

Goetzinger., *et al.* demonstrated that low first-trimester PAPP-A levels are associated with the development of preeclampsia [24].

Spencer., *et al.* showed that in the preeclampsia group, compared to the controls, maternal serum levels of PAPP-A, free β-hCG, activin A and inhibin A were significantly increased [25].

Kirkegaard., *et al.* revealed that low serum levels of PAPP-A and free β-hCG are independent biomarkers associated with preterm delivery (< 37 weeks) [26].

The confirmation of chromosomal abnormalities is done by karyotyping of foetal cells from the chorionic tissue or amniocytes, cultured from amniotic fluid. Karyotyping mostly required invasive procedures, like amniocentesis and chorionic villous biopsy.

The screening tests were helpful as they decreased the need for invasive prenatal testing. At the same time, it was essential to identify an ideal screening test that best represented the confirmative test result [27-30].

## Conclusion

The percentage of chromosomal abnormalities in pregnant women has been growing in the last three years, and this worrying fact imposes the need to find out the cause of this phenomenon.

Additionally, food content, air quality, and soil tests are needed to determine the association with the increased risk of our town.

The dual marker test is a very important tool for practitioners, because fetal chromosomal abnormalities can be diagnosed early in gestation and provide enough time for a confirmative test and if the risk of pregnancy is confirmed, it can be terminated in time.

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## Conflict of Interest

None declared.

## Ethical Approval

Not required.

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