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Comparison of First Trimester Screening for Down's Syndrome Using Free β-hCG and PAPPA Levels between Spontaneous and IVF Pregnancies: A Mini-Review

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ABSTRACT

First Trimester Screening (FTS) tests are used to assess adverse outcomes in pregnancy. Large bodies of studies have reported different levels of these biomarkers in normal pregnancies than in vitro fertilization (IVF), as an important treatment for infertility. The purpose of this review is the investigation of the β-hCG and PAPPA values during the screening of the first trimester of pregnancy and its consequences.

Keywords: β-hCG: Beta Human Chorionic Gonadotropin; FTS: First-Trimester Screening; IVF: In Vitro Fertilization, PAPPA: Pregnancy-Associated Plasma Protein-A (PAPPA)

INTRODUCTION

Today, prevention and prognosis of adverse pregnancy outcomes are critical, challenging issues for society, scientific community and family. In addition to parental information and psychopathology, socioeconomic factors represent the main etiology for creating a reliable prenatal prognostic protocol [1]. Trisomy 21 (Down's syndrome) is the most common prenatal chromosomal abnormality with a prevalence of about 1:600-800 in pregnancies worldwide with fetal nuchal translucency (NT) thickness detected by ultrasound and measurement of maternal serum levels of Beta human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11 to 13 weeks in about 90% of pregnancies by the false positive rate of about 5% [2]. In 2018, among the screening results of 28,726 Taiwanese women, 891 positive cases of trisomy 21 (97.5%) and 3.5% false positive rate were reported. Screening of the first trimester of pregnancy had a high rate of diagnosis rate and reduces unnecessary invasive tests for pregnant women [3]. Younesi et al. [4] in a retrospective cohort study, on 197,210 cases of pregnancy screened in the first trimester from March 2015 to February 2016, proposed a novel parameter namely the ratio of fβ-hCG multiple of the median (MoM) value to PAPP-A MoM value (fβ-hCG MoM: PAPP-A MoM) to delicately categorize first trimester screening results in a way that reduce of false negatives rate. The intermediate risk group is important as 23 out of 45 false negatives (FN) (the range between 1: 250 to 1: 1100), by applying the proposed index of this study, the ratio of (fβ-hCG MoM: PAPP-A MoM) and subsequent decision about noninvasive prenatal testing (NIPT), 8 out of 23 FN cases were considered [4]. Compared with the current policy, the novel proposed approach appears to be performing better and can be applied to improve the screening program guidelines without incurring additional costs and unnecessary anxiety for families.

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FIRST TRIMESTER SCREENING IN IVF AND SPONTANEOUS CONCEPTIONS

Comparison between maternal serum screening biomarkers in Spontaneous and IVF Conceptions in 2018 in Ontario, Canada showed that there was no significant difference in circulating α-fetoprotein (αFP), PAPP-A and β-hCG levels in the first trimester as well as non-conjunctival estradiol in the second trimester, total β-hCG and inhibin-A between two groups [5]. In another study conducted in 2019, the means of the MoM of PAPP-Ain IVF pregnancies with the fresh (1.19 ± 0.6), in the frozen embryo transfer (1.03±0.5) that were slightly lower in compared with natural conceptions (1.33 ± 0.7). But when the medians of the MoM of PAPP-A, β-hCG and their distributions were compared across the mode of conception, there were no differences between IVF pregnancies and spontaneous pregnancies. These results support the notion that uncomplicated singleton IVF pregnancies have similar first trimester screening profiles to spontaneous conceptions [6]. Moreover, it has been shown that the lower PAPP-A and higher levels of fβ-hCG in compared to normal pregnancies in the single IVF pregnancies [7], which can be related to different placentation in intracytoplasmic sperm injection (ICSI) technique because of alterations in the oocyte cytoplasm. In contrast, more recently, it has been found that PAPP-A levels were higher in IVF twins compared with spontaneous twins, while there was no difference in β-hCG levels between two groups [8]. In this line, another study declared an association between low PAPP-A and fetal death [9]. The results of the available data suggest that these biomarkers may need to be adjusted in assisted reproductive technology (ART) conceptions. First-trimester screening for trisomy in pregnancies with a vanishing twin should rely on a combination of maternal age, fetal nuchal translucency thickness and serum level of free β□hCG, as in singleton pregnancy, without the use of serum PAPP-A measurement. Alternatively, PAPP□A can be included only after appropriate adjustment for the interval between estimated gestational age at fetal demise and blood sampling [10].

β-HCG

Maternal hCG secreted by trophoblastic cells is used as a predictor of pregnancy prognosis in normal pregnancy and IVF cycle [11]. However, the relationship between primary hCG levels and pregnancy outcomes in the IVF cycle is not fully understood. In this, regard the results of different studies are controversial for different reasons, such as demographic characteristics, the stage of the transferred embryos, and cryopreservation. In 2017, it was shown that the mean of initial β-hCG in women who had a clinical pregnancy was significantly higher in frozen cycles than in fresh cycles [11]. Assess of 177 IVF cycles from 2009 to 2014 also showed that β-hCG level can predict the outcomes in singleton and twin IVF pregnancies 13 days after embryo transfer. In addition, singleton pregnancies with a β-hCG <85 mIU/mL had an 89% risk of first trimester loss, whereas a β-hCG>386 mU/mL had a 91% chance of a live birth. Twin pregnancies with a β-hCG<207 mIU/mL had only 33% chance of delivering twins and 55% risk of having a vanishing twin; whereas a β-hCG>768 mIU/mL was associated with 81% chance of live twin birth and a low risk (19%) of having a vanishing twin. The loss of singleton and twin pregnancies, and also vanishing twin are well known in pregnancy (IVF), and this reality brings uncertainty and anxiety to the couples regarding outcomes of their pregnancies. Hence, a test performed early in pregnancy that could predict the outcomes might be reassuring. Therefore, the initial β-hCG level is considered a reliable predictor of IVF outcomes [12]. In 2020, Wang et al. [13] found that increasing serum level of β-HCG led to a reduction in chemical pregnancies, an increase in multiple pregnancies, a decrease in ongoing pregnancies and ectopic pregnancies. The cut-off value of serum β-HCG levels for the prediction of biochemical pregnancy were 213/15, 986.65, and 2206.5 IU/L for singleton, multiples, and twins or triplets, respectively. Serum β-HCG level 14 or 12 days after embryo transfer (3 or 5 days after oocyte retrieval) predicts biochemical / clinical pregnancy with robust sensitivity and specificity [13]. In 2017, β-HCG enhancement with birth weight, but not gestational age at delivery in singleton IVF pregnancies was also associated. The infant gender, gestational age, and the type of embryo transfer (fresh vs. freeze-thawed) were significantly associated with birth weight, and β-HCG rising was slower among subjects delivering an infant with low birth weight (LBW) or small for gestational age (SGA). These findings suggest that events in pre-implantation period may have a long-term effect on fetal health and affect serum levels of HCG hormone, which reflect the early trophoblast differentiation and placentation [14]. While the findings of this study are interesting, further studies are needed to clarify the cellular mechanism of these clinical observations. Furthermore, the routine serum screening of various biomarkers such as PAPP-A and β-hCG levels in the first trimester can also be used as a tool of risk identification of preterm delivery, which could be significantly lower in preterm delivery [15]. Despite the PAPP-A and β-hCG levels in diabetic pregnancies were lower than normal pregnancies, this screening could not be used to identify preeclampsia (PE), intrauterine growth restriction (IUGR), macrosomia, and preterm birth in diabetic pregnant women [16]. In addition, a cohort study from 2016 to 2018 in Iran showed that βhCG>3 (MOM) causes 5.65 times increase, and PAPP-A<0.4 (MOM) causes 2.9 times increase in the chance of developing preeclampsia (PE) [17]. It is also worth mentioning that the adverse pregnancy outcomes such as preterm delivery, low birth weight (LBW), and preeclampsia (PE) may be associated with low levels of PAPP-A and β-hCG [18]. However, more studies are needed to explain the relationship between first-trimester screening markers and neonatal outcomes.

PAPP-A

PAPP-A is another first trimester screening parameter that has the substantial effect on pregnancy outcomes [19]. Many recent studies support the role of PAPP-A in the diagnosis of the increased risk and adverse pregnancy outcomes. In addition to chromosomal abnormalities, preeclampsia (PE), intrauterine fetal death (IUFD), and pregnancy loss have been associated with low PAPP-A in maternal serum, and have a strong positive predictive value for SGA and IUGR [1,20]. Based on the previous reports, because of the low sensitivity and accuracy of clinical examinations as well as arterial Doppler for predicting fetal growth restriction (FGR), 14.5% of neonates are born with SGA which may lead to over-estimation of cases who are SGA. In recent years, researchers declared that the use of biochemical markers, maternal medical history, and some dynamic vascular parameters during the first and second trimesters are undeniable factors to predict fetal growth. Given that the mean level of PAPP-A in neonates with SGA was lower than other neonates, the results of a study conducted in 2020 showed that the cutoff point was 0.75 MoM, while lower levels with high sensitivity and specificity could predict SGA [21]. However, another study showed the higher levels of cut-off point (1.06 MoM). this conflict results may be caused by a variety of factors, such as differences in the tools used to measure, the influence of genetic factors, and different gestational ages [21]. Together, a strong consensus among researchers is that there is a strong association between PAPP-A levels and birth weight, and this factor is a reliable indicator for screening and predicting the outcomes of pregnancy. However, further studies are requested to fully understand the related mechanism of action to exploit its potential.

FIRST TRIMESTER SCREENING (FTS) AND LONG-TERM OUTCOMES FOR MOTHERS AND THEIR OFFSPRING

Some hormones measured during pregnancy are linked directly to certain hormone-sensitive cancers. According to a cohort study conducted in Canada, among 67,7247 pregnant women, 7231 breast cancers, 515 ovarian cancers, 508 endometrial cancers, and 4,105 thyroid cancers were observed. β-hCG greater than the 95th percentile (MoM) was associated with a doubling risk of endometrial cancer, low AFP at the fifth percentile or less MoM had conferred a moderately greater risk of thyroid cancer, but low PAPP-A levels at the fifth percentile or less MoM was statistically significantly associated with breast cancer [22]. According to the evidence-based reports, women with abnormal hormone levels during pregnancy may be at a greater future risk of certain types of hormone-sensitive cancers. PAPP-A value as well as clinical data collected at birth from 2004 to 2010 in 988 patients, after 7 years of follow-up in 2015, showed that low serum levels of PAPP-A in the first trimester of pregnancy have been associated with short stature in offspring and subsequently the increased risk of maternal diabetes in future [20]. These researches could play a substantial role in better understanding of metabolic disorders and should be considered by obstetric care professionals in order to inform patients about possible further complications, making it enact prevention measures, and ultimately improving women's health [23].

CONCLUSION

The serum level of specific biochemical markers during first trimester screening is different between normal and IVF pregnancies in various studies. These markers, in addition to helping early diagnosis and timely prevention, may be useful for mothers and their offspring in assessing long-term risks and upcoming consequences. However, more studies are needed to perform in this field.

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CONFLICT OF INTERESTS

These authors had no conflict of interests.

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