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Pregnancy outcomes regarding maternal serum AFP value in second trimester screening

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Abstract

Aim: The aim of this study was to evaluate the predictive value of α-fetoprotein in maternal serum (MS-AFP) as a marker for diverse pregnancy outcomes.

Methods: The study was based on pregnancy and delivery data from 5520 women between 1999 and 2014 at University Hospital of Zurich (UHZ). Inclusion criteria: both MS-AFP and pregnancy outcome were known for the same pregnancy. Pregnancy outcomes and characteristics such as fetal malformation, intrauterine fetal death (IUFD) and intrauterine growth retardation as well as maternal age, weight before pregnancy, gestational age (GA) at delivery, newborn weight, length and head circumference were analyzed with respect to the MS-AFP value. MS-AFP value was categorized into three groups: elevated MS-AFP > 2.5 multiples of the median (MoM), normal 0.5–2.49 MoM and decreased < 0.5 MoM.

Results: Newborn weight (g) and length (cm) were significantly lower in the elevated MS-AFP ($P < 0.001$) group, and infants had 1 week lower GA at delivery ($P < 0.05$). In the group of elevated MS-AFP ($n = 46$), 26.1% of pregnancies were significantly related to adverse pregnancy outcomes, such as fetal malformations, fetuses small for gestational age (SGA) and IUFD. Adverse pregnancy outcomes of 5.6% were registered in the group of normal MS-AFP and 7.3% in the group of low MS-AFP ($P < 0.05$).

Conclusion: MS-AFP level in the second trimester is still an important indicator of fetal surface malformations; however, ultrasound still outweighs as a screening method. Nevertheless, pregnant women with elevated MS-AFP values and with no sonographically detected fetal malformations should additionally receive the third trimester ultrasound examination to exclude other possible complications of pregnancy.

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Keywords: Intrauterine fetal death; intrauterine fetal growth retardation; maternal serum AFP; pregnancy outcome; small for gestational age.

Introduction

The era of prenatal screening for life-threatening congenital anomalies began in the 1970s with the investigation of increased levels of α-fetoprotein (AFP) in amniotic fluid and maternal serum in pregnancies affected by fetal open neural tube defects (NTDs) [1]. Since then AFP-Test has been part of routine prenatal preventive care, at least in more economically developed countries.

AFP is a glycoprotein, member of the albuminoid gene family [2, 3]. It is produced in early pregnancy by fetal liver and yolk sac [4]. AFP synthesis in the proliferating fetal liver increases through the 20th week of gestation and thereafter remains fairly constant until the 32nd week [4, 5]. AFP is excreted into fetal urine and transported into maternal serum through the placenta or by diffusion across the fetal membranes [3]: leakage from fetal serum and cerebrospinal fluid (NTD); exposure of blood vessels in extruding viscera, leading to transudation of AFP; expedited protein filtration and passage into urine (congenital nephrosis); impaired fetal swallowing or digestion in amniotic fluid (GI anomaly) and altered or obstructed transplacental passage, such as in placenta accreta [6]. As a result, an elevated amount of AFP is estimated in maternal serum in case of open NTD, omphalocele, gastroschisis, congenital renal disease, esophageal atresia or fetal distress situations such as threatened abortion and fetal demise. Nevertheless, rise of AFP concentration may be observed in multiple pregnancies [7]. AFP level might also be influenced by gestational age (GA) at the time of assessment, maternal weight, racial origin, smoking, parity and *in vitro* fertilization [8, 9]. Increased AFP values were additionally registered at placenta-mediated adverse pregnancy outcomes such as preeclampsia, intrauterine fetal growth restriction (IUGR), intrauterine fetal death (IUFD) abruptio placentae, preterm birth and oligohydramnios [10–16], possibly due to anomalies of placentation or ischemic placental disease [17]. As a result of placental hypoxia and apoptosis, some products of the

syncytiotrophoblast such as human chorionic gonadotropin and inhibin A, as well as AFP, a product of the yolk sac and fetal liver, may reach the circulation in greater quantities than in normally developed placentas [18]. However, AFP regulating function during pregnancy and AFP involvement in the regulation of placental growth remains controversial and relatively unknown [15].

Due to ultrasound, diagnosis of the majority of NT and fetal surface defects is possible in early pregnancy; therefore, maternal serum alpha-fetoprotein (MS-AFP) screening is losing its value. Different countries have diverse regulations regarding MS-AFP.

In Canada it was already concluded that the primary use of MS-AFP for open/closed NTDs screening should be discontinued with the limited clinical exceptions of pregnant women with a pre-pregnancy body mass index >35 kg/m^2 or when geographical or clinical access factors limit timely and good quality ultrasound screening at 18–22 weeks' gestation [19]. MS-AFP testing is not required in the UK when the routine ultrasound screening is performed [20]. In the USA, NTD screening is optional [21]. Swiss health insurance covers the screening of MS-AFP, which is optional in the second trimester.

Therefore, the aim of this study was to evaluate the predictive value of MS-AFP as a marker for possibly different pregnancy outcomes and its use in the prenatal care.

Materials and methods

The retrospective cohort study comprised pregnancy and delivery data of 5520 women at the University Hospital of Zurich (UHZ) between 1999 and 2014. Pregnancies with the known outcomes and measured MS-AFP-value in the second trimester were included. Patients with multiple gestations and pregnancies with incomplete data were excluded from the study.

MS-AFP analysis was performed at UHZ between 13 and 18 weeks of gestation and the costs were covered by health insurance. MS-AFP value >2.5 multiples of the median (MoM) was defined as elevated, 0.5–2.49 MoM as normal and <0.5 MoM as low. Fetal malformations such as NTDs, surface defects, structural anomalies and genetic disorders or IUFD and small for gestational age newborns (SGA, newborn's weight below or equal to the 5th percentile for GA according to local reference curves) were registered. Correlation between the MS-AFP value and pregnancy complications was analyzed. Newborns with malformations were excluded from the SGA group. Pregnancy characteristic such as maternal age, weight before pregnancy, GA at delivery, newborn weight, length and head circumference were analyzed.

Statistical data analysis was performed using standard statistical programs (SPSS, Chicago, IL, USA; EXCEL, Redmond, WA, USA). The χ^2 test was used to compare fetal malformations, IUFD and SGA in the groups of elevated, normal and low MS-AFP. The one-way analysis of variance (ANOVA) test was performed to evaluate the differences of maternal age, weight before pregnancy, newborn weight, length, head circumference and GA in the determined AFP groups. A P-value of <0.05 was considered statistically significant.

Results

Maternal and newborn characteristics are presented in Table 1. Any significant differences between AFP groups regarding maternal age, maternal weight, newborn weight percentile and length percentile as well as newborn head circumference were found. Newborn weight and length ($P<0.001$) as well as GA at delivery ($P<0.05$) were lower in the group of elevated AFP.

In the group of elevated MS-AFP (n=46), 12 (26.1%) pregnancies were significantly related to adverse pregnancy outcomes, such as malformations, SGA and IUFD. Adverse pregnancy outcomes of 5.6% (n=286) were registered in the group of normal and 7.3% (n=10) in the group of low MS-AFP ($P<0.05$).

The rate of IUFD was significantly higher in the group with elevated MS-AFP. Corresponding outcome was found in 21.7% (n=10), 2.2% (n=109) and 0.6% (n=1) in elevated, normal and low MS-AFP groups ($P<0.00001$), respectively. Distribution of adverse pregnancy outcomes

Table 1: Maternal and newborn characteristics.

AFP value	>2.49 MoM (n=46)	0.5–2.49 MoM (n=5036)	<0.5 MoM (n=138)	P-value
Maternal age (years)	31.5	30.8	30.6	>0.05
Maternal weight (kg)	64.7	65.5	71.5	>0.05
Newborn weight (g)	2873	3274	3285	<0.001
Newborn weight (‰)	46.3	53.4	55.5	>0.05
Newborn length (cm)	46.8	49.0	48.9	<0.001
Newborn length (‰)	48.5	53.5	55.0	>0.05
Head circumference (cm)	33.8	34.4	34.7	>0.05
GA (weeks)	37.4	38.6	38.5	<0.05

Table 2: Distribution of adverse pregnancy outcome and fetal death regarding the MS-AFP value.

MS-AFP value	>2.49 MoM	0.5–2.49 MoM	<0.5 MoM	P-value
n = 5220	46 (0.9%)	5036 (95.9%)	138 (3.2%)	
SGA	5 (10.9%)		231 (4.4%)	<0.05
Hydrops	0	3	0	
Fetal malformation count	7 (15.2%)	60 (1.2%)	2 (1.4%)	<0.0001
-Genetic disorders	3 (42.9%)	6 (9.5%)	0	<0.0001
-*Spina bifida*	2 (28.6%)	2 (3.2%)	0	<0.0001
-Surface defects	0	9	1	
-Brain malformations	1	8	0	
-Cardiac malformations	0	9	0	
-Kidney malformations	0	9	0	
-Multiple malformations	1	3	0	
-Other malformations	0	14	1	

and fetal death regarding the MS-AFP value is presented in Table 2. Genetic disorders and *spina bifida* were found to be significantly more frequent in the group of elevated MS-AFP ($P < 0.0001$). However, there was no statistically significant difference between other malformations in different MS-AFP groups. *Spina bifida* and fetal surface defects in the groups of normal and decreased MS-AFP were also found. Significantly more SGA newborns were found in the group of elevated MS-AFP ($P < 0.05$).

Discussion

This study was performed to evaluate the predictive value of MS-AFP as a marker for screening possibly different pregnancy outcomes and its use in the prenatal care. Weight and length of newborns were lower in the group of an elevated AFP. Statistically significant differences were found only in grams and centimeters, but not in percentiles, probably because of lower GA. Significantly more malformations, especially *spina bifida*, and SGA newborns were found in the group of an elevated AFP too. On the other hand, *spina bifida* and surface defects were also found in the group of normal MS-AFP. In the group of elevated MS-AFP, significantly more IUFD were found. This difference between IUFD in different MS-AFP groups could be caused due to an increased count of fetal malformations in the group of elevated AFP and only one fetus with IUFD had no malformations. Results of the Yaron study [22] were different. It was noticed that pregnancies with unexplained mid-trimester elevation of MS-human chorionic gonadotropin (hCG) and/or MS-AFP were at increased risk of IUFD. The positive correlation between elevated MS-AFP level and SGA has already been described in the studies of Poon and Lesmes. They found that pregnant women with SGA neonates, in the absence of preeclampsia, had an increased uterine artery pulsatility index (UtA-PI) as well as MS-AFP levels at 19–24 weeks of gestation [23, 24]. The study of Barta et al. speculated that MS-AFP could be used as a marker for determination of fetal condition when following SGA fetuses [25]. Sharony et al. [26] recently reported that MS-AFP and amniotic fluid AFP ratio might serve as a predictor of SGA and GA at delivery, and the higher the ratio, the lower the birth weight and GA. Although many of the associations between mid-trimester MS-hCG and/or MS-AFP levels and adverse pregnancy outcomes are statistically significant, the sensitivity and positive predictive value are too low for them to be clinically useful as screening tests. In the study of Dugoff [27], it was proposed that all women with unexplained elevation of mid-trimester MS-AFP levels should receive an increased fetal surveillance. It was suggested that ultrasonography is the most cost-effective approach and should be used as the initial diagnostic examination. However, the current retrospective study has some limitations. First of all, the study population with elevated MS-AFP was low. Furthermore, other maternal factors such as PIGF, MS-hCG and UtA-PI that could predict SGA were not analyzed.

In Switzerland, Canada, USA and UK, MS-AFP screening for NTDs is optional. It is universally agreed that ultrasound technology has better chances as a screening method; however, it may be worth to perform MS-AFP screening test for NTDs in addition to ultrasound, especially in teaching hospitals, where the young examiners are inexperienced. This combined screening approach could help avoid missed NTDs and other fetal surface defects. MS-AFP included in “combined” screening tests could also alert an increased risk of adverse pregnancy outcomes in the third trimester. We suggest that pregnant women with an elevated mid-trimester MS-AFP value, but without any fetal malformations detected by ultrasound

at the 20–24 weeks of gestation, should receive an additional third trimester ultrasound examination, to exclude IUGR and other adverse pregnancy outcomes.

Author's statement

Conflict of interest: Authors state no conflict of interest.

Material and methods: Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human subject use has complied with all the relevant national regulations, and institutional policies, and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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