Prenatal Serum Alpha-Fetoprotein Screening in Pregnant Women

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Summary An investigation of maternal serum alpha-fetoprotein (AFP) screening of 3,762 women was performed. There were 2.07% of pregnancies screened between 16 and 25 weeks with the serum AFP level above 2.5MoM. In the meanwhile 2.07% of the population screened had an AFP level below 0.25MoM. Four fetuses with open neural tube defects and three with other anomalies (one with omphalocele, one with hydrops fetalis and one with multiple anomalies) were all detected. One case of open neural tube defects (NTD) with serum AFP measured at 12 weeks' gestation and three with closed NTD were missed. Sixty-three percent of twin pregnancies and 12% of low birth-weight infants in the population also had serum AFP levels above 2.0MoM. No significant difference exists in mid-trimester serum AFP among gestational diabetes mellitus, low birth-weight, macrosomia, intrauterine growth retardation, or normal pregnancies.

(*J Formosan Med Assoc* 1988 ; 87 : 745-50)

Key words: *Maternal AFP screening, neural tube defects*

The elevation of amniotic alpha-fetoprotein (AFP) levels in pregnancies with anencephaly and open spina bifida was first observed by Brock and Sutcliffe in 1972 [1]. Subsequently, Leek and Brock demonstrated that the level of AFP in maternal serum was also increased [2,3]. During the past decade the measurement of maternal serum AFP has become an efficient screening tool for fetal neural tube defects. Raised serum AFP may show an increased risk towards preeclampsia and some other pathological conditions [4-7]. This study is designed to screen neural tube defects in Chinese women with maternal serum AFP.

MATERIALS AND METHODS

From January to May, 1986, 3,762 pregnant women between 10 and 40 weeks gestation were included in this study. Most of them had their serum AFP measured on the first antenatal visit. The gestation was calculated from the date of the last menstrual period or by ultrasound scan. Serum AFP levels were measured by radioimmunoassay using the Clinical Assays™ Gamma Dab® [I^{125}] AFP RIA kit Baxter Healthcare USA) and expressed as ng/ml. The normal median value was obtained from our preceding study of uncomplicated Chinese pregnant women [8]. Patients with serum AFP levels above 2.5 multiples of median (MoM) were subjected to an ultrasound examination to detect multiple pregnancy, congenital anomalies and duration of gestation. A repeat sample was requested after exclusion of multiple pregnancy and incorrect dating. Termination of pregnancy was carried out if fetal abnormality was diagnosed. The outcome of all pregnancies was ascertained.

RESULTS

The percentage of maternal population at various stages of gestation in relation to raised and decreased levels of AFP is presented in Table 1. A total of 1,595 patients were screened between 16 to 25 weeks of gestation. There were 2.07% and 4.83% among them with serum levels above 2.5MoM and 2.0MoM respectively, and 7.96% and 2.07% of pregnancies had

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Received: November 20, 1987. Revised: March 26, 1988. Accepted: April 25, 1988.
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Table 1. Distribution of Elevated and Decreased MSAFP in Relation to Gestational Age

Gestation Age (weeks)	Median (ng/ml)	≥2.5 MoM	≥2.0 MoM	<0.5 MoM	<0.25 MoM	No. of cases
10	3.2	27.27	27.27	31.82	31.82	22
11	3.7	38.89	38.89	16.67	16.67	36
12	13.1	14.34	17.00	28.34	17.41	247
13	19.8	4.28	9.74	21.62	10.93	421
14	22.8	3.71	10.86	14.57	8.68	350
15	27.6	5.18	10.36	9.96	6.77	251
16	38.6	1.95	4.30	10.55	5.47	256
17	43.3	2.13	5.30	10.28	1.77	282
18	53.1	.91	4.78	4.35	0.43	230
19	59.2	1.06	1.06	9.57	2.13	188
20	61.8	2.17	4.35	5.07	0.72	138
21	79.5	.75	7.89	5.26	0.88	114
22	100.3	.77	5.31	5.31	1.77	113
23	114.9	4.12	8.25	10.31	1.03	97
24	137.8	0.00	2.35	7.06	1.18	85
25	144.2	3.23	6.45	6.45	2.15	92
26	169.9	0.00	0.00	8.70	0.00	69
27	159.4	.66	7.32	4.88	3.66	82
28	182.1	.90	3.23	6.45	2.15	62
29	174.3	0.00	3.03	4.55	.00	66
30	190.5	0.00	6.33	5.06	2.53	79
31	229.2	4.62	6.15	7.69	1.54	65
32	216.4	1.96	5.88	5.88	3.92	51
33	226.0	0.00	1.89	7.55	0.00	53
34	205.2	0.00	1.59	6.35	3.17	63
35	252.1	0.00	0.00	8.33	0.00	60
36	188.4	3.77	7.55	5.66	0.00	53
37	206.6	0.00	3.70	5.56	1.85	54
38	196.8	0.00	2.17	8.70	2.17	46
39	120.5	12.00	24.00	0.00	0.00	25
40	109.0	16.67	25.00	16.67	16.67	12

MoM = multiple of median, unit: %
MSAFP = maternal serum alpha-fetoprotein

Table 2. Distribution of MSAFP in A Population Screened between 16 and 25 Weeks of Gestation

Gestation weeks	≥2.5 MoM	≥2.0 MoM	<0.5 MoM	<0.25 MoM	No. of cases
16-25	2.07%	4.83%	7.96%	2.07%	1595

MoM = multiples of median
MSAFP = maternal serum alpha-fetoprotein

serum AFP levels less than 0.5MoM and 0.25MoM (Table 2). There were 8 neural tube defects and 3 other anomalies (one with encephalocele, one with hydrops fetalis and one with multiple anomalies). Seven out of eight neural tube defects had raised serum AFP at the cut-off value of 2.5MoM. It failed to detect three cases with closed defects and one anencephalus having an AFP measured at 12 weeks of gestation (Table 3). The 3 other anomalies had the raised serum AFP above 2.5MoM. Three cases with trisomy 21 were identified with the confirmation of genetic determination. Two of them had decreased AFP levels. The remaining one with duodenal atresia did not exhibit decreased AFP which was measured as early as 12 weeks of gestation.

In the population screened between 16 and 25 weeks, 70% (7/10) of twin pregnancies had serum AFP levels above the cut-off level of 2.0MoM and 73% (8/11) of impending fetal demise had levels below 0.5MoM. Although low-birth-weight pregnancies have higher serum AFP values, only 11.8% (4/34) of the cases can be identified by serum AFP at the cut-off point of 2.0MoM during 16 to 25 weeks of gestation. No significant difference in mid-trimester serum AFP values was shown among IUGR, macrosomia, gestational diabetes mellitus or normal pregnancies

Table 3. Birth Outcome and MSAFP in NTD, Trisomy 21 and other Anomalies

Cases	Sampling	AFP		Birth	
	weeks	MoM	ng/ml	Weight (g)	Weeks
NTD					
Meckle Sd A	27	6.30	1004.4	1550	27
Meckle Sd B	22	5.70	471.1	1650	33
	27	2.80	447		
	31	1.90	436		
Encephalocele	22	0.92	92.5	2100	40
	40	1.64	176		
Anencephalus A	12	0.45	5.9	1000	30
Anencephalus B	18	7.62	404.9	130	20
Anencephalus C	23	2.96	340.5	1400	34
Meningomyelocele A	12	0.40	21.4	3100	41
Meningomyelocele B	38	1.39	273.6	2650	40
	40	2.00	218.7		
Trisomy 21					
A*	12	1.6	20.9	2500	26
B	16	0.14	5.5	3050	39
C	19	0.54	31.8	3250	40
Other anomalies					
Omphalocele	16	7.23	279.1	1420	33
	33	3.92	886		
NIHF	14	6.76	154.2	1000	19
	18	4.60	244.5		
	19	3.71	220.1		
Multiple Anomalies	25	3.73	538.5	3100	35

NTD = neural tube defects, Sd = syndrome
NIHF = nonimmunologic hydrops fetalis
* with duodenal atresia

Table 4. Distribution of MSAFP in Complicated and Normal Pregnancies Screened between 10 and 15 Weeks of Gestation

	MSAFP						
Situations	≥2.5 MoM	≥2.0 MoM	0.5 - 2.0 MoM	<0.5 MoM	<0.25 MoM	MoM median±SD	Total cases
IUGR	5 (6.6)	11 (4.5)	49 (64.5)	16 (21.0)	8 (10.5)	1.16 ± 0.86	76
LBW	5 (13.9)	12 (33.3)	20 (55.6)	4 (11.1)	2 (5.6)	1.75 ± 1.59	36
Macrosomia	0 (0.0)	0 (0.0)	22 (91.7)	2 (8.3)	0 (0.0)	1.10 ± 0.47	24
Twin	5 (41.7)	8 (66.7)	4 (33.3)	0 (0.0)	0 (0.0)	2.59 ± 1.29	12
IUFD	0 (0.0)	0 (0.0)	7 (70.0)	3 (30.0)	0 (0.0)	0.71 ± 0.22	10
Abortion	1 (11.1)	1 (11.1)	2 (22.2)	6 (66.7)	4 (44.4)	0.85 ± 1.65	9
GDM	0 (0.0)	0 (0.0)	8 (80.0)	2 (20.0)	2 (20.0)	0.88 ± 0.45	10
Normal	50 (6.1)	90 (11.0)	574 (70.3)	152 (18.6)	92 (11.3)	1.21 ± 1.27	816

IUGR = intrauterine growth retardation, IUFD = intrauterine fetal death (beyond 20 weeks)
GDM = gestational diabetes mellitus, LBW = low birth weight, ( ) = %

Table 5. Distribution of MSAFP in Complicated and Normal Pregnancies Screened between 16 and 20 Weeks of Gestation

	MSAFP						
Situations	≥2.5 MoM	≥2.0 MoM	0.5 - 2.0 MoM	<0.5 MoM	<0.25 MoM	MoM median ± SD	Total cases
IUGR	0 (0.0)	2 (3.3)	51 (85.5)	7 (11.7)	2 (3.3)	1.05 ± 0.51	60
LBW	1 (4.8)	2 (9.5)	17 (81.0)	2 (9.5)	2 (9.5)	1.08 ± 0.59	21
Macrosomia	0 (0.0)	0 (0.0)	18 (94.7)	1 (5.3)	0 (0.0)	0.95 ± 0.31	19
Twin	2 (28.6)	4 (57.1)	3 (42.9)	0 (0.0)	0 (0.0)	1.86 ± 0.73	7
IUFD	0 (0.0)	1 (20.0)	4 (80.0)	0 (0.0)	0 (0.0)	1.26 ± 0.49	5
Abortion	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	2 (100)	0.00 ± 0.00	2
GDM	0 (0.0)	0 (0.0)	6 (100)	0 (0.0)	0 (0.0)	1.18 ± 0.25	6
Normal	9 (1.3)	20 (2.9)	615 (70.3)	62 (8.9)	14 (2.0)	1.06 ± 0.54	697

IUGR = intrauterine growth retardation, IUFD = intrauterine fetal death (beyond 20 weeks)
GDM = gestational diabetes mellitus, LBW = low birth weight, ( ) = %

Table 6. Distribution of MSAFP in Complicated and Normal Pregnancies Screened between 21 and 25 Weeks of Gestation

	MSAFP						
Situations	≥2.5 MoM	≥2.0 MoM	0.5 - 2.0 MoM	<0.5 MoM	<0.25 MoM	MoM median ± SD	Total cases
IUGR	0 (0.0)	1 (3.6)	25 (89.3)	2 (7.1)	1 (3.6)	0.91 ± 0.43	28
LBW	0 (0.0)	2 (15.4)	10 (76.9)	1 (7.7)	0 (0.0)	1.23 ± 0.64	13
Macrosomia	0 (0.0)	1 (12.5)	7 (87.5)	0 (0.0)	0 (0.0)	1.25 ± 0.53	8
Twin	0 (0.0)	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	1.57 ± 0.40	3
IUFD	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	1.54 ± 0.60	2
Abortion	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	1.12 ± 0.00	1
GDM	0 (0.0)	0 (0.0)	2 (80.0)	0 (20.0)	0 (20.0)	1.29 ± 0.33	2
Normal	5 (1.6)	15 (4.8)	275 (88.7)	20 (6.5)	3 (1.0)	1.06 ± 0.44	310

IUGR = intrauterine growth retardation, IUFD = intrauterine fetal death (beyond 20 weeks)
GDM = gestational diabetes mellitus, LBW = low birth weight, ( ) = %

(Tables 4-6).

DISCUSSION

AFP was discovered in 1956 as a new protein with alpha-mobility [9]. It presents in fetal and embryonic tissues, disappears in the corresponding adult tissues, but reappears in certian types of tumors [10]. There are two distinct routes for AFP into the maternal circulation; a direct one across the placenta and an indirect one via amniotic fluid and fetal membranes. AFP levels in maternal serum are much lower than in amniotic fluid throughout pregnancy. In fetuses with open neural tube defects, exomphalos and congenital skin defects, there is exposure of fetal capillaries to amniotic fluid. Thus the levels of fluid AFP might be increased.

Maternal serum AFP should be screened in mid-trimester. However, this is a preliminary study. We studied patients between 10 and 40 weeks of gestation with the majority of cases in mid-trimester. At the cut-off level of 2.5MoM, 2% of the population screened will require an ultrasound examination. It is reasonable to have a population with such a distribution. All the open neural tube defects and abdominal wall anomalies were detected. Recently it was observed that low maternal serum AFP values are correlated with aneuploidy [11]. Two cases with trisomy 21 had low serum AFP. One of trisomy 21 with concomitant duodenal atresia was measured in the first trimester with a normal level.

As well as screening for neural tube defects, AFP may be useful as a predictor of fetal well-being [12]. AFP is also associated with intra-uterine growth retardation and an increased incidence of preeclampsia, while serum AFP values were lower in diabetic than in nondiabetic women [13]. At this investigation there was no significant difference between them and normal pregnancies. Our results may be different if a larger population were screened. Multiple pregnancy is also associated with a raised AFP level which may be related to the increase in the size of the placenta. Sixty-three per cent of our twin pregnancies have elevated serum AFP levels. These results are in agreement with the report of Ghosh et al [14].

Early detection of fetal anomalies is always desirable. The cost-effectiveness of the screening program should not be judged on the basis of detected numbers of neural tube defects alone. It also provides the identification of subsequent pregnancy complications and reassurance of the pregnancies.

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產前母血清甲型胚胎蛋白篩檢

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神經管缺損及某些胎兒異常的懷孕其羊水及母血清中的甲型胚胎蛋白（alpha-fetoprotein）濃度有顯著上升。從1986年1月至5月，總共有3762例懷孕週數由10週至40週之孕婦接受篩檢。大多數的婦女是在第一次產前檢查時，抽血以放射免疫分析法測量。分析各個懷孕週數中，數值偏高或偏低者所佔的人口的比例，即需要進一步做超音波檢查或羊水分析者所佔的人口比例。母血清甲型胚胎蛋白篩檢在懷孕第二期時最有意義。有1595例孕婦在懷孕16週至25週篩檢，其中2.07%母血清甲型胚胎蛋白濃度大於或等於2.5倍中數。同時亦有2.07%的孕婦其值小於0.25倍中數。8例懷神經管缺損的胎兒，其中4例開放型者血清值均超過2.5倍中數。3例封閉型者及1例無腦兒未能檢測出來。此無腦兒例乃早在懷孕12週時接受篩檢。1例臍膨出，1例胎兒水腫及1例多發畸型者，其血清值均超過2.5倍中數。所有開放型的神經管缺損病例及腹壁異常的病例均已測出。最近報導血清值低下與染色體數異常有關。3例是21三染色體症，其中2例有明顯血清值降低的情形；另一例同時合併有十二指腸閉鎖，在懷孕12週檢查血清值並未下降。多胞胎懷孕其胎盤較大，母血清濃度亦較高。雙胞胎懷孕在16週至25週接受篩檢時有70%的血清值高於2倍中數。將來發生胎死腹中或流產者血清值有73%低於0.5倍中數。雖然低出生體重的懷孕在篩檢時，血清值有較高的情形，但其中只有11.8%的病例超過2倍中數。妊娠性糖尿病及巨嬰症懷孕篩檢時其濃度可能會下降；在本實驗中濃度減少與正常懷孕比較未達統計上的意義。母血清甲型胚胎蛋白篩檢工作，可以早期發現神經管缺損的異常和某些有問題的懷孕。

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受文日期　民國76年11月20日　修正日期　民國77年3月26日　接受日期　民國77年4月25日

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