

Fetal Defect Marker Proficiency Test Mailout from September 12, 2006 October, 2006

Dear Laboratory Director,

Below you will find a summary and critique of the Proficiency Testing mail-out from September 12, 2006 for Fetal Defect Markers, including AFP, uE3, hCG, and dimeric inhibin-A. Your laboratory's results and grades are printed on a separate sheet; also included are the grades from the previous two PT events. Please review and sign your evaluation. Retain the signed packet in your files. You will need it for your next laboratory survey to demonstrate participation in the NYSPT program.

Maternal Serum: Summary of Sample Results

Samples *N = 32	Sample #	MS 196	MS 197	MS 198	MS 199	MS 200
	Gestational Age (weeks)	19.0	20.0	18.0	17.0	16.0
Maternal Race	Ethnic Group	Black	White	Hispanic	Asian	White
Maternal Weight	Pounds (lbs)	200	125	130	125	135
Maternal Age	Years	22	40	24	35	20
Alpha-Fetoprotein (AFP)	Mean ng/mL	116.51 ±11.20	36.92 ±2.82	60.38 ±4.56	98.88 ±8.28	30.44 ± 2.70
	MoM	2.58 ±0.23	0.58 ±0.04	1.29 ±0.08	2.34 ±0.15	0.87 ±0.06
Unconjugated Estriol (uE3)	Mean ng/mL	2.91 ± 1.37	2.15 ±1.01	4.12 ±2.09	2.12 ±1.01	1.15 ±0.51
	MoM	1.19 ±0.29	0.62 ±0.18	1.79 ±0.43	1.19 ±0.33	0.82 ±0.27
human Chorionic Gonadotrophin (hCG)	Mean IU/mL	20.53 ±3.11	29.55 ± 2.62	17.37 ± 1.74	23.63 ±2.11	34.30 ± 4.79
	MoM	1.19 ±0.16	1.53 ±0.19	0.78 ±0.11	0.88 ±0.11	1.06 ±0.15
Dimeric Inhibin-A (DIA)	Mean pg/mL	212.35 ±20.64	340.42 ±35.73	161.22 ±17.10	176.00 ±16.07	170.50 ±17.11
	MoM	1.42 ±0.14	1.67 ±0.22	0.92 ±0.12	0.99 ±0.12	0.96 ±0.13
Neural Tube Screen (Positive, Negative)	Pos (+) or Neg. (-)	Pos. 56%	Neg. 100%	Neg. 100%	Neg. (B) 60%	Neg. 100%
	Further Action R,U,A	R = 17% U = 30% A = 27%	NFA	NFA	R = 23% U = 26% A = 19%	NFA
	NTD Risk	275	7,558	5,000	350	10,000
Trisomy-21 Screen (Positive, Negative)	Pos (+); Neg.(-)	Neg. 100%	Pos. 100%	Neg. 100%	Neg. 100%	Neg. 97%
	Recommended Action	NFA	U = 89% A = 83%	NFA	NFA	NFA
	Risk Est.	10,000	14	10,500	4,600	1,871
2. <u>Quad Test</u>	Pos (+); Neg. (-).	Neg. 100%	Pos. 100%	Neg. 100%	Neg. 100%	Neg. 100%
	Recommended Action **	NFA	U = 83% A = 83%	NFA	NFA	NFA
	Risk Est.	12,000	10	14,700	9,350	4,494
Trisomy-18 Screen (Positive, Negative)	Pos (+)/Neg. (-)	Neg.	Neg.	Neg.	Neg.	Neg.
	Risk Est.	10,000	725	10,000	10,000	10,000

*N=total numbers may vary since some labs do not test all analytes. The values represent the All-Lab consensus based on the arithmetic mean ±SD; (B) = borderline positive or negative, risk reflects central tendency (Modal number for Down positive/borderline screen). NFA=no further action; FA=further action (see below); R = repeat; U = ultrasound, and A = amniocentesis. **This percentage is normalized to labs requesting further action. † Insulin Dependent Diabetic

Maternal Serum Analytes: Summary of Test Results

N = 31 All-Lab Consensus Values.

<u>Sample #</u>	<u>Summary Comments (Mock specimens):</u>
MS 196 Wk 19.0	Specimen MS196 was obtained from a 22 year old Afro-American woman with a body weight of 200 lbs. Her family had a history of pregnancy complications. The patient was gravida 1, parity 0. Her MSAFP specimen was deemed screen positive for NTD (56% of labs) as shown in Fig. 1&3. Her screen was negative for trisomy-21 and trisomy 18 with all labs in agreement. The NTD recommended follow-up was as follows: Repeat sample 17%, ultrasound 30%, and amniocentesis 27%. Note that this patient's sample required two algorithm adjustments: race, and body weight. This maternal serum sample (MOM = 2.58) was matched to amniotic fluid specimen AF196 which was borderline positive (Fig. 2; MoM = 1.86).
MS 197 Wk 20.0	Specimen MS197 originated from a 40 year old Caucasian woman with a body weight of 125 lbs. She had no family history of adverse pregnancy outcomes. She was gravida 2, parity 1. Her sample was determined to be screen negative for NTD with no further action recommended. However, this specimen screened positive for trisomy-21 (100% consensus). The triple test recommended follow-up was as follows: ultrasound 89% and amniocentesis 83%, while the quad test was ultrasound 83% and amniocentesis 83%. Her trisomy-18 screen was determined to be negative in 100% of the participating laboratories. This specimen had no amniotic fluid matched counterpart.
MS 198 Wk 18.0	Specimen MS198 originated from a 24 year old Hispanic woman with a body weight of 130 lbs. She was gravida 3, parity 2 and related no family history of pregnancy complications. Her NTD screen was negative and 100% of the labs requested no further action. Both the trisomy 21 and 18 assessments were screen negative. MS198 had no paired amniotic fluid sample.
MS 199 Wk 17.0	Specimen MS199 originated from a 35 year old Asian woman with a body weight of 125 lbs. She gave no family history of NTD or aneuploid pregnancies. Her sample MS199 was determined to be a borderline negative screen for NTD, but screen negative for both trisomy 21 and 18. All labs agreed with the trisomy screens. Recommendations for further action from labs reporting a borderline negative NTD (60%) were: repeat-23% ultrasound 26%, and amniocentesis, 19%. However, 60% of the labs reported no further action. Following amniocentesis, the MS199 specimen (MOM=2.34) was paired with AF199 specimen which also proved to be elevated (AFAFP MOM=2.6). See AF199 critique below for more details.
MS 200 Wk 16.0	Specimen MS200 was obtained from a 20 year old Caucasian woman with a body weight of 135 lbs. She had no history of miscarriage in her family. She was gravida 1, parity 0. Her gestation appeared unremarkable at the time of specimen collection. Her sample was deemed screen negative for NTD with no further action recommended. This specimen also screened negative for trisomy 21 and trisomy-18 (100% consensus). MS200 did not have a matched amniotic fluid specimen.

Notice of Gravida/Parity Clarification for Present and Future Mailouts:

This notice regards the demographic data provided for the mock patients in the FEDM program. For the sake of uniformity, it will be understood that gravida indicates a pregnant woman and parity is the state of having given birth to an infant or infants. Thus, a gravida = n, indicates number (n) of times pregnant including the present one; a gravida = 2 indicates that the women was pregnant once before in addition to her present pregnancy. Parity = 1 indicates the patient already has one child; also, multiple birth is considered as a single parity.

Example: A woman of gravida = 3, parity = 2 indicates that the pregnant woman has been pregnant twice before, and has two children.

AMNIOTIC FLUID AFP (NTD-analysis):

N=30; All-Lab Consensus Values

<u>Sample</u>	<u>Values</u>	<u>Summary Comments:</u>
AF 196 Wk 19.0	AFP= 15.21 ± 2.1 µg/ml MOM= 1.86 ± 0.22	This AF sample was intended as a borderline positive AF-AFP specimen in the upper gestational screening range. All labs indeed agreed with the borderline positive assessment. The sample was paired to maternal serum specimen (MS196 = 2.58) which appeared elevated.
AF 197 Wk 20.0	AFP= 3.9 ± 0.3 µg/ml MOM= 0.59 ± 0.06	This AF sample was targeted and achieved a normal AF-AFP value in the upper gestational age screening range. All labs classified this sample as a normal specimen. This sample was not paired to a maternal serum sample.
AF 198 Wk 19.0	AFP= 6.4 ± 0.6 µg/ml MOM= 0.78 ± 0.08	This AF sample was targeted for a normal AF-AFP value in the upper gestational age screening range. All labs classified it as a normal AFAFP specimen. This sample had no maternal serum counterpart.
AF 199 Wk 17.0	AFP= 31.3 ± 3.7 µg/ml MOM= 2.60 ± 0.26	This AF sample was targeted and achieved an elevated AF-AFP mass value in the routine gestational age screening range. All labs classified this sample as an elevated specimen. The sample was matched to maternal serum counterpart MS199 which was borderline elevated (MOM=2.34).
AF 200 Wk 18.0	AFP= 4.1 ± 1.2 µg/ml MOM= 0.39 ± 0.07	This AF sample was intended as a normal AF-AFP specimen in the routine gestational age screening group. All labs categorized this sample as a normal AF-AFP specimen. The AF sample was not matched to MS200.

Fetal Defect Proficiency Test Mailout 9/12/06 Critique of Maternal Serum and Amniotic Fluid Values:

The all-lab results of the targeted values for the NTD and the Trisomy Screen were within expectation of our projected target values, risks, and outcomes. As displayed in the above tables, maternal sera MS196 and MS199 were targeted as positive and borderline positive for NTD, respectively (Fig. 1 and 3). Sample MS196 was obtained from an Afro-American woman with a history of family pregnancy complications; her AF specimen also produced a borderline elevated AFP value (see Figure-2) MoM = 1.86. Specimen MS196 screened positive for NTD, and the lab recommended actions were somewhat conservative and, correspondingly the NTD screen indicated a 1:275 risk for open neural tube defects (ONTD). The recommended action for the MS196 specimen was: sample repeat, 17%; ultrasound; 30%; and amniocentesis, 27%. In view of these MS screen results, the paired amniotic fluid AFP specimen proved to be only borderline elevated indicating the need for both Ache and fetal hemoglobin analysis. Interestingly, the MS196 positive screen was only a 56% all-lab consensus. This consensus may have been influenced by the borderline positive AFAFP results (MOM = 1.86). Correspondingly, the MS199 specimen also screened borderline negative for NTD with a 60% all-lab consensus. Even though MS199 failed to achieve the 80% consensus criteria in our testing program, the paired AF-AFP measurement clearly indicated that this mock patient had a presumptive risk for NTD. It is interesting that the all-lab median cutoff value for MSAFP is 2.5 MOM. Finally, specimens MS197, MS198, and MS200 were targeted and achieved negative screens for NTD, and all labs recommended no further action. Of these samples, MS197 did produce a positive screen for Trisomy-21 which is discussed below.

As mentioned above, amniotic fluid sample AF196 was matched to NTD positive screen sample MS196 and showed a borderline elevated AFAFP (MOM = 1.86) in comparison to the maternal serum sample (MOM = 2.58) of this patient (Figure 1&2). A subsequent mock Ache analysis proved negative as a follow-up procedure for specimen AF196. Moreover, slightly increased levels of fetal hemoglobin were detected in the mock AF196 specimen indicating that a small fetal-maternal bleed (or placental tear) might have occurred at some previous time. Subsequent diagnostic ultrasound of this mock patient did not demonstrate the presence of a neural tube anomaly and a diagnostic Ache band was not present following gel electrophoresis.

The MS199 sample screened NTD positive for a American women of Asian descent. Interestingly, the overall prevalence rate of NTDs in China is 1.2/1000 births (USA = 1.5/1000), with the prevalence rate of anencephaly, spina bifida, and encephalacele being 0.5/1000, 0.6/1000, and 0.2/1000, respectively (see Ref. 23). Although the annual rates of NTDs in China have presented an overall declining trend, it is still higher than in other countries in the same time period tested. However, most countries have not yet instituted periconceptual folic acid supplementation. Although the MS199 all lab median risk for NTD was calculated at 1 in 350, an Alpha risk computer calculation produced a 1 in 80 risk. Her body weight was in the normal range and no algorithm corrections were required. Her all-lab AF AFP MOM consensus was 2.60 which would be a positive screen in most prenatal programs. Her all-lab DS risk was quite low (4600 to 10,000), although her age was 35 years. Although a greater risk of DS would be expected from the maternal age alone (1 in 300), the risk is, in fact, lower due to the levels of the four analytes used in the quad test.

Regarding the trisomy screen, MS197 was intended to produce a positive Trisomy-21 (T21) screen with both the triple and quad testing platforms, which indeed was the case. The labs reporting either triple or quad testing concluded that sample MS197 was T21 screen positive (100% consensus). Further action recommended for the MS197 specimen was determined as 89% ultrasound (US) and 83% amniocentesis (AM) for labs using the triple screen, and 83% US and 83% AM for labs employing the quad test. Further recommended action on MS197 reflected the severity of the risk ratio assessment of 1:14 risk from the triple test versus 1:10 risk from the quad test, regardless of the software program employed. Note from the data distribution graphs comparing the triple with the quad test (Figs. 5 and 6) that the MS197 point cluster in the quad assay was lower and more compact than the cluster in the triple test. Overall, both triple and quad tests clearly signaled a very high risk for Down syndrome.

Sample MS197 (see above) was notable in that the specimen screened positive for trisomy-21 in a 40 year old patient together with an age alone risk. This mock Caucasian patient was gravida 2, parity 1, and reported no history of trisomy disorders in her immediate and extended family. A maternal age of 40 years already placed this patient at an increased risk for trisomy pregnancy. The mock physician had requested an immediate biochemical screen (triple or quad) and ultrasound due to her maternal age, (40 yr) and the gestational age (20 weeks) of her pregnancy. The subsequent biochemical MS results for the Trisomy screen revealed the following: AFP-MOM = 0.58 uE3; MOM = 0.62; hCG-MOM = 1.53; and Inhibin MOM = 1.67 (Triple Risk = 1:14; Quad Risk = 1:10); thus, the AFP, uE3, and hCG, and inhibin measurements were each consistent with a classical DS risk assessment. Her prenatal screening risk of Down syndrome was indeed greater than expected from maternal age alone (1 in 80) and the four analytes drove the risk even greater.

The performances of the various kits for maternal serum analytes (AFP, uE3, hCG) are presented in a bar graph form (Figures 7-9) for each of the five MS samples. As shown in the MS-AFP graph, AFP mass measurements among the individual kits largely agreed, although Bayer-Centaur was slightly higher while DPC Immulite and Beckman Unicel were lower for some samples. For uE3, the all lab median was higher than 1.0 (1.3) due to the labs employing DPC Immulite and DPC Immulite 2000 which yielded values averaging nearly two times higher than the median (see dotted line). In contrast, Diagnostic Systems Lab RIA/EIA results were at the mean level while Beckman Access measured uE3 values nearly one-third lower than the median. These results continue to demonstrate some inherent differences as to how these assays recognize the uE3 in our mock sample preparations. Regarding the hCG kits, laboratories employing Abbott AxSYM displayed much higher mean values reaching 1.5 times higher than the medians while Bayer-Centaur, Immulite, and Beckman Access yielded mean (1.0) hCG values. In order to enhance uniformity among the various kits employed to measure hCG, we incorporate an intact (total) hCG recombinant analyte into our PT specimens. Labs lacking peer group companions and in-house assays will continue to be deemed non-gradable (NG) for hCG as well as other analyte groups as the situation dictates.

The bar graph in Figure 10 is provided to display kit performance among the amniotic fluid (AF-AFP) test samples. As shown in the amniotic fluid bar graph, overall kit performance approached that observed with the maternal serum samples. While Bayer-Centaur, and to a lesser extent Abbott-AxSYM Kits kits were higher, Beckman Access and DPC Immulite were lower than the all-lab mean as seen in previous mailouts. It is of interest that amniotic fluid specimens, AF199 and AF200, yielded the lowest values with the DPC Immulite Kits as compared to all other kits employed (Fig. 10). The reason for this kit performance anomaly has yet to be determined and could be sample-associated. As always, please be advised that these samples are derived from actual AF samples, and therefore these results are directly relevant to patient screening.

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New References (Suggested reading):

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Abstracts

A). Screening Abstract “Pick-of-the-Month”:

Title: Second-trimester prediction of severe placental complications in women with combined elevations in alpha-fetoprotein and human chorionic gonadotrophin.

Source: American Journal of Obstetrics & Gynecology. 194 (3): 821-827, 2006.

Authors: Alkazaleh, Fawaz. Chaddha, Vandana. Viero, Sandra. Malik, Aasim. Anastasiades, Colleen. Sroka, Hana. Chitayat, David. Toi, Ants. Windrim, Rory C. Kingdom, John C.

Address:

Abstract: **Objective:** The purpose of this study was to determine the ability of uterine artery Doppler and placental ultrasound to identify adverse clinical outcomes attributable to severe placental dysfunction in women with second-trimester unexplained elevated maternal serum screening of alpha-fetoprotein and human chorionic gonadotropin. **Study Design:** Fifty singleton pregnancies with elevated alpha-fetoprotein (3.5 multiples of median [range 2.1 to 10.5]) and human chorionic gonadotropin (5.3 multiples of median [range 2.5 to 21.7]) and a normal fetal anatomical ultrasound were prospectively evaluated with placental ultrasound and uterine artery Doppler at referral between 19 and 23 weeks' gestation. **Results:** Abnormalities in both placental ultrasound and uterine artery Doppler (n = 24) predicted preterm delivery less than 32 weeks from any cause (n = 24) (75% sensitivity, 75% positive predictive value; likelihood ratio positive predictive value; likelihood ratio positive 3.1 [2.0 to 5.01]), and intrauterine growth restriction with absent/reversed end-diastolic flow (n = 17) (sensitivity 94%, positive predictive value 67%, likelihood ratio positive 3.9 [2.0 to 6.2]). Ischemic-thrombotic pathology was present in 88% of placentas examined (n = 32). **Conclusion:** Uterine artery Doppler and placental morphology identified most pregnancies with combined abnormal maternal serum screening destined to result in extremely premature delivery and/or perinatal death. Abnormal maternal serum screening reports could include a recommendation for placental ultrasound testing when no fetal explanation has been identified.

B). Case History “pick-of-the-month:

Title: Congenital sialoblastoma (embryoma) associated with premature centromere division and high level of alpha-fetoprotein.

Source: Prenatal Diagnosis. 25(8): 687-689, 2005.

Authors: Ozdemir, Ismail. Simsek, Enver. Silan, Fatma, Demirci, Fuat.

Abstract: Sialoblastoma is a rare, locally aggressive, and potentially malignant perinatal salivary tumor that predominately affects the parotid glands. To date, 29 cases of sialoblastoma have been reported. We report a further case of sialoblastoma diagnosed at 37 weeks of gestation presenting with novel findings that are the premature centromere division and a high level of alpha-fetoprotein.

C). News of Note: Abstracts of New Markers and /or New Testing Agents:

1). Title: Pregnancy-associated plasma protein A and alpha-fetoprotein and prediction of adverse perinatal outcome.

Source: Obstetrics & Gynecology. 107(1): 161-166, 2006.

Authors: Smith, Gordon CS. Shah, Imran. Crossley, Jennifer A. Aitken, David A. Pell, Jill P. Nelson, Scott M. Cameron, Alan D. Connor, Michael J. Dobbie, Richard.

Abstract: **Objective:** To describe the association between pregnancy associated plasma protein A (PAPP-A), alpha-fetoprotein (AFP) and adverse perinatal outcome. **Methods:** We conducted a multicenter prospective cohort study of 8,483 women delivering a small for gestational age infant, delivering preterm, and stillbirth were related to maternal serum levels of PAPP-A and AFP. **Results:** Women with a low PAPP-A were not more likely to have elevated levels of AFP. Compared with women with a normal PAPP-A and a normal AFP, the odds ratio for delivering a small for gestational age infant for women with a high AFP was 0.9 (95% confidence interval [CI] 0.5-1.6), for women with a low PAPP-A was 2.8 (95% CI 2.0-4.0), and for women with both a high AFP and a low PAPP-A was 8.5 (95% CI 3.6-20.0). The odds ratio for delivering preterm for women with a high AFP was 1.8 (95% CI 1.3-2.7), for women with a low PAPP-A was 1.9 (95% CI 1.4-22.0). These interactions were statistically significant for both outcomes

($P = .03$ and $.04$, respectively). There was a nonsignificant trend toward a similar interaction in relation to stillbirth risk. Of the women with the combination of a low PAPP-A and high AFP, 32.1% (95% CI 15.9-52.4) delivered a low birth weight infant. **Conclusion:** Low maternal serum levels of PAPP-A between 10 and 14 weeks and high levels of AFP between 15 and 21 weeks gestation are synergistically associated with adverse perinatal outcome. **Level of Evidence:** II-2.

2) Title: Elevated circulating insulin-like growth factor binding protein-1 is sufficient to cause fetal growth restriction.

Source: Endocrinology. 147(3): 1175-1186, 2006.

Authors: Watson, Carole S. Bialek, Peter. Anzo, Makoto. Khosravi, Javad. Yee, Siu-Pok. Han, Victor KM.

Abstract: IGF binding protein-1 (IGFBP-1) inhibits the mitogenic actions of the IGFs. Circulating IGFBP-1 is elevated in newborns and experimental animals with fetal growth restriction (FGR). To establish a causal relationship between high circulating IGFBP-1 and FGR, we have generated transgenic mice using the mouse alpha-fetoprotein gene promoter to target overexpression of human IGFBP-1 (hIGFBP-1) in the fetal liver. These transgenic mice (AFP-BP1) expressed hIGFBP-1 mainly in the fetal hepatocytes, starting at embryonic d 14.5 (E14.5), with lower levels in the gut. The expression peaked at 1 wk postnatally (plasma concentration, 474 ± 34 ng/ml. At birth, AFP-BP1 pups were 18% smaller [weighed 1.34 ± 0.02 g compared with 1.62 ± 0.04 g for wild type (WT); $P < 0.05$], and they did not demonstrate any postnatal catch-up growth. The placentas of the AFP-BP1 mice were larger than WT from E16.5 onwards (150 ± 12 for AFP-BP1 vs. 100 ± 5 mg for WT at E16.5; $P < 0.05$). Thus, this model of FGR is associated with a larger placenta, but without postnatal catch-up growth. Overall, these data clearly demonstrate that high concentrations of circulating IGFBP-1 are sufficient to cause FGR.