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The Anatomic Basis of Maternal Serum Screening

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ABSTRACT

Fetal serum markers, such as alpha fetoprotein (AFP), must traverse one of two very different pathways to reach maternal serum, either from fetus to amnion fluid, membranes and decidua or from fetal to maternal circulation through the placental villi. Alpha fetoprotein usually enters the amnion fluid through body wall defects uncovered by skin or through urine. Placental AFP leakage may be from villous hemorrhage or injury. These observations from anatomic pathology suggest that biochemical markers may exist to identify the source of elevated maternal serum AFP.

The purpose of this report is to convey to the laboratory specialist in maternal serum screening the insight resulting from the study of the relevant pathologic anatomy. The physiology will not be considered in any detail. The basic anatomic reality is that fetal blood and serum markers must reach the maternal circulation through one of two major anatomic routes. The most direct route is through the placental villi where maternal and fetal circulations are, of necessity, in close proximity. The alternative route requires escape from the fetus into the amnion fluid, and then through the avascular epithelium of amnion and chorion into the vascularized, decidualized, maternal endometrium.

The fetal route usually begins with a breach of the fetal skin. This is the basis of maternal serum alpha fetoprotein (MSAFP) screening for neural tube and body wall defects. If skin covers the defect, alpha fetoprotein (AFP) will not be elevated in amnion fluid or maternal serum, and, hence, a fundamental limit to AFP screening. Skin may cover a body wall defect of any size or at any location, including neural tube defects, and omphalocele (figures 1, 2, and 3).

Serum markers can also escape from the fetus through the kidney, because urine is the major source of amnion fluid. Elevated amnion fluid AFP has been reported in congenital nephrotic syndrome in which protein would be expected to leak from fetal blood to urine.[1] Renal injury (cystic dysplasia) from urethral obstruction may also be detectable by maternal serum AFP. Such detection is important because corrective fetal surgery must be performed prior to permanent renal damage.[2] A case was presented in which the MSAFP was 2.6 (MOM), which prompted a level 2 ultrasound showing urethral obstruction with minimal renal abnormality. Fetal urinalysis followed which yielded

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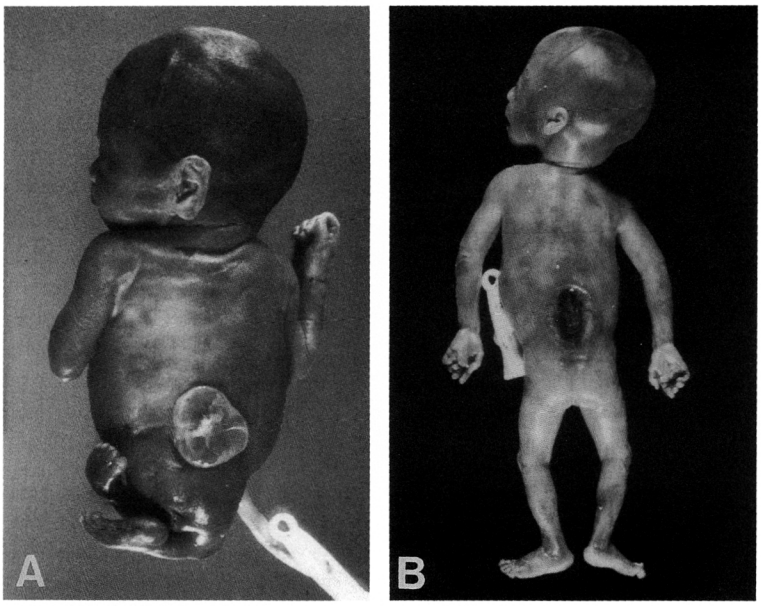

FIGURE 1A. Fetus (22 week gestation) with a skin covered lumbar myelomeningocele and caudal dysplasia. The maternal serum alpha fetoprotein was 0.8 multiples of the median (MOM). 1B: Fetus (20 week gestation) with membrane covered lumbar myelomeningocele. Maternal serum alpha fetoprotein was 3.9 multiples of the median (MOM).

isotonic urine, a bad prognostic indicator, and abortion, rather than surgery, was elected. The kidneys did show early dysplasia. The relationship of renal injury to maternal serum AFP values needs further study. A final role of renal leakage is in cases in which a known metabolic defect would be expected to produce an abnormal urine metabolite. This metabolite could find its way from amnion fluid to maternal serum.

The second major route between fetal and maternal blood is across the micron distances from fetal placental capillaries to maternal intervillous placental blood flow. In some cases, this could occur by hemorrhage, as evidenced pathologically by the commonly found intervillous thrombus.[3,7] However, indirect evidence suggests that other types of villous injury such as ischemia or inflammation may also cause AFP to leak into maternal blood.[4,5] Thus, serum AFP may be a marker of multiple pregnancy complications.

Knowing which pathway led to an elevated MSAFP could be very useful. The high false positive rate in screening for neural tube defects could be reduced if a second marker demonstrated that the AFP elevation was due to villous hemorrhage or injury, rather than a fetal anomaly. The distinction from villous hemorrhage might be made by demonstrating fetal red blood cells (although there is a false positive rate in the second trimester) or red cell precursors. Fetal serum from villous injury would have a very different path of physical barriers than serum that had to travel through amnion and chorion. In addition, villous injury should release markers of fetal trophoblast injury such as human placental lactogen or chorionic gonadotrophin.

Yet another value to knowing the pathway of MSAFP is in elucidating the relationship of MSAFP to fetal death.[6] This association could be due to the diffusion of AFP through dead tissue into amnion fluid, as hemolysis is seen to stain tissue throughout the fetus who has remained dead *in utero* for hours. If, however, the AFP were a marker for the injury causing death, (the maternal circulation

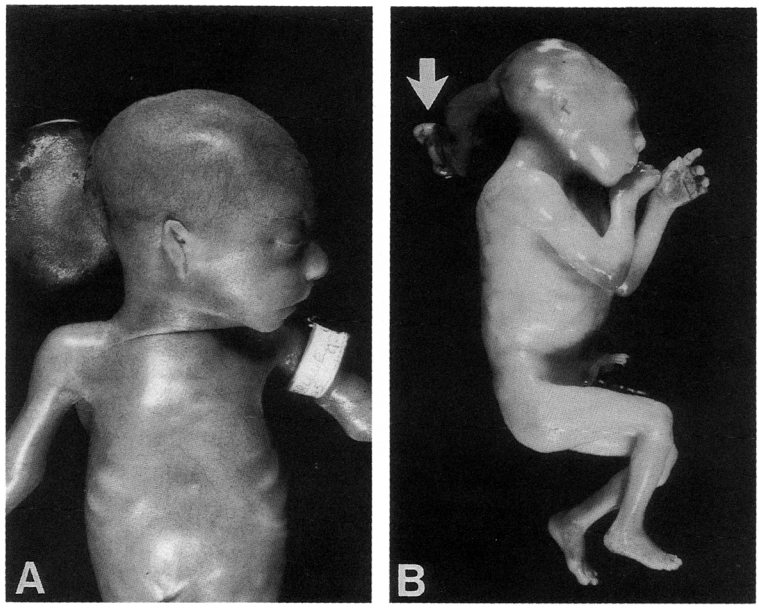

FIGURE 2A. Fetus (20 week gestation) with skin covered encephalocele. Maternal serum alpha fetoprotein unknown. 2B: Fetus (18 week gestation) from an insulin dependent diabetic mother with a membrane covered portion of the encephalocele (arrow). The maternal serum alpha fetoprotein was 2.1 multiples of the median. (MOM).

maintains the viability of the placenta), a different pattern of fetal serum markers might be elevated in maternal serum.

Ultimately, the cooperation of chemist (to know about potential unique fetal chemical markers), fetal physiologist (to understand the partitioning of those markers), and anatomic pathologist (to correlate the serum findings with the morphologic and pathologic process), should provide laboratory testing to refine further the meaning of a positive (high) MSAFP screen. If this can be done on the same blood sample before final reporting, maternal anxiety can be reduced with no risk and low cost. This

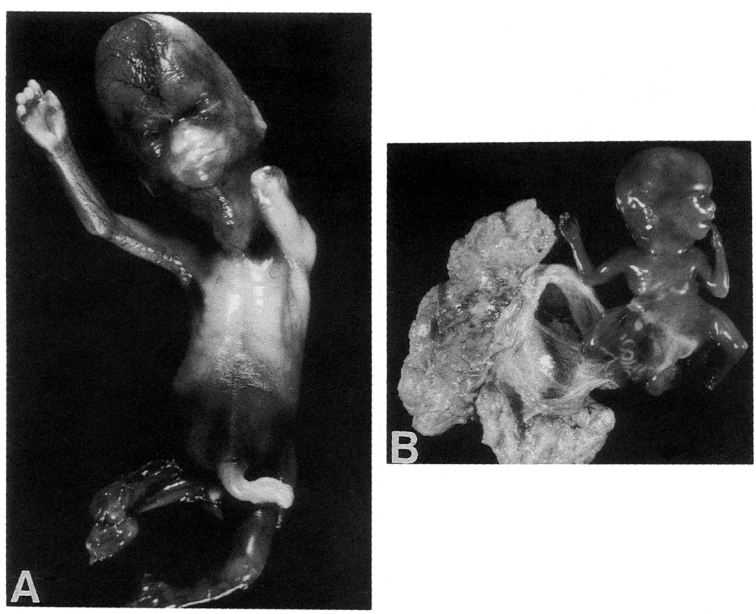

FIGURE 3A. Fetus (16 week gestation) with skin covered omphalocele. Maternal serum alpha fetoprotein unknown. 3B: Fetus (20 weeks gestation) with early amnion rupture sequence with a large membrane covered abdominal wall defect. Maternal serum alpha fetoprotein was 29 multiples of the median (MOM).

might also permit lowering risk cut offs to increase total detection. At best, new insight and potential new therapies need to be developed for obstetrical disease based on maternal serum screening.

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