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IN UTERO DEFECATION: A NEW CONCEPT*

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According to the current concepts, the human fetus does not defecate, and passage of meconium into the amniotic fluid is an indicator of fetal distress. However, the literature consists of reports in which fetal defecation is postulated to be a physiologic event. In light of these reports and our observations, we have developed the hypothesis that fetal defecation is a physiologic event independent from fetal distress and associated with a clearance mechanism of the amniotic fluid. This hypothesis has been proved by a series of experimental studies. We have shown that goat fetuses defecate the contrast medium into the amniotic cavity in the absence of fetal distress. We have clearly demonstrated for the first time the transport of radioactive meconium through the gastrointestinal tract into the amniotic fluid by using a radiopharmaceutical agent. It is known that the clearance mechanism of the amniotic fluid is supressed under fetal distress conditions. We suggest that meconium stained amniotic fluid is not related to meconium passage due to fetal distress; rather, it reflects impaired clearance of amniotic fluid containing meconium because of physiologic in utero defecation. This is discussed in detail with a review of the literature. *Key words: fetal physiology, in utero defecation.*

The human gastrointestinal tract has secretory, digestive, absorptive, and barrier functions. In addition, it also serves as an endocrine organ and as a part of the immunologic system. Its development is mainly completed during the fetal period, and an alimentary system is ready to meet the demands of nutrition after birth. This development is under the influence of endogenous and exogenous factors. The genetic endowment of the organism, regulated by an intrinsic "biologic clock", controls this sequential development, which is modulated by exogenous factors in the form of luminal influences such as amniotic fluid and various systemic influences (maternal, fetal, and neonatal neuroendocrine milieu)[1].

The gastrointestinal tract appears morphologically prepared for oral feeding by the end of the second trimester. Bowel peristalsis is reported as early as the 8th week of gestation, while swallowing is observed at the 16th week[2]. Intestinal motor activity of the gut moves the intraluminal contents from one specialized region of the gut to the next. Infants of less than 30 weeks' gestation exhibit disorganized random peristaltic contractions, and those of 30-33 weeks have short bursts of motor activity called "fetal complexes". Thereafter, co-ordinated migrating motor complexes are present[3]. This peristaltic development is also responsible for the

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intestinal passage of the fetus[4]. Today, there is no doubt that the intraluminal content is transported by gastrointestinal peristalsis during intrauterine life[2, 4-6]. This peristalsis increases with gestational age. In general, the older the fetus, the more intraluminal content descends through the gastrointestinal tract.

The intraluminal content (meconium) originates from secretions and desquameted cells of the fetal digestive tract as well as, to a lesser degree, from swallowed amniotic fluid. Meconium was named by Aristotle, who thought that it kept the fetus asleep in the uterus. Hippocrates stated that the presence of meconium in the fetal intestine was proof of the fact that the "fetus sucks inside the womb"[2]. From studying the meconium patterns of fetuses, it was found that major changes occur in the distribution of meconium within the intestine between 13 and 21 weeks of gestation. Meconium first becomes detectable to the eye from the 13th week and, until the 18th week, it is predominantly in the small intestine, with some accumulation in the colon. After the 21st week, all fetuses showed a build up of meconium in the rectum[7-9]. The chemical composition of meconium also changes substantially throughout gestation due to numerous transformations of the gastrointestinal system with regard to motility and absorption functions[10, 11]. Its water content varies from 70 to 80 percent and 80 percent of its dry weight is made up of mucopolysaccharides. It contains small quantities of serum proteins and many enzymes. Among them, those originating from the digestive tract, such as disaccharidases, dipeptidases, lysosomal enzymes and trypsin, constitute the majority[12, 13].

The development of the gastrointestinal tract for digestive, absorptive, secretory and endocrine functions occurs simultaneously with that for motility function. Digestion and absorption of carbohydrates, proteins and lipids through different parts of the gastrointestinal tract are shown in the human fetus[14-16]. The fetus gut secretes several hormones which have trophic, secretory and motor effects[17]. Analysis of enterochromaffin cells in the bovine fetus gut revealed that serotonin may be the chemical inducer of muscular motility[18]. Epithelial absorptive and secretory cells are found in the human fetus intestine starting from the 8th week of gestation[19].

As outlined above, the human gastrointestinal tract undergoes numerous transformations, and the fetus can perform a wide spectrum of physiologic functions including sucking, swallowing, intestinal transport, and absorption as well secretory and endocrine functions. However, the last step of nutrition, in other words in utero defecation (the passage of meconium into the amniotic fluid), is not accepted as a physiologic function of the fetus. According to the current concepts, in utero defecation results in meconium-stained amniotic fluid and is believed to be associated with fetal distress as first described in 1858[20]. However, some authors suggest that meconium passage into the amniotic fluid alone is not necessarily a sign of fetal distress, as no definitive cause of fetal distress was found in 12 to 25 percent of deliveries complicated with meconium-stained amniotic fluid[5-7, 20, 21].

Additionally, meconium-stained amniotic fluid was described as a common obstetric finding with an incidence ranging between seven and 30 percent of all deliveries[6]. But, of the infants born with meconium-stained amniotic fluid, only 2.1 percent have developed meconium aspiration syndrome[23]. The high incidence of meconium-stained amniotic fluid versus the low incidence of complications and the absence of maternal and fetal distress conditions in a quarter of the cases render the current belief about in utero defecation questionable.

In light of these findings, we have developed the hypothesis that fetal defecation is a physiologic event independent from fetal distress and associated with a clearance mechanism of the amniotic fluid. A series of experimental studies was performed on this hypothesis. These studies are outlined below.

Study I

An experimental study was performed to investigate gastrointestinal motility and meconium passage, with simultaneous blood gas measurements, in the fetuses of eight pregnant goats at 110 to 114 days' gestation (full term = 147 to 155 days). With the goats under halothane anesthesia, a nasogastric tube and a heparinized central venous catheter were inserted into the fetuses. Twenty-four hours after surgery, 10 ml of gastric juice from the fetus was replaced with a nonhydrosoluble contrast medium, and serial roentgenograms and blood samples (for PO_2, and PCO_2 measurement) were taken every four hours. All fetuses began to pass the contrast medium into the amniotic cavity within 16 to 22 hours, and central venous blood gas values were normal[5].

Study II

An experimental study was performed to investigate the excretion function of the liver, gastrointestinal motility, and in utero defecation by radionuclide techniques in 24 New Zealand white rabbit fetuses at 25 days' gestation (full term = 31 to 32 days). Technetium-99 m (^{99m}Tc)-HIDA (a derivative of iminodiacetic acid) (0.1 ml) containing 1 millicurie (mCi) of radioactivity was injected into the gluteus muscle of each fetus which had been exposed through the uterus. After replacing the fetus and uterus into the abdomen, and beginning one hour after injection, a live fetus was killed each hour for 24 hours. Tissue samples from the lung, heart, stomach, kidney, bladder and liver; meconium in the proximal, mid and distal bowel, and amniotic fluid were taken. The radioactivity of each sample was determined by a gamma counter and the percentage uptake per gram of tissue was calculated. The very low radioactivity levels detected in the stomach, kidney and bladder indicated the in vivo stability of ^{99m}Tc-HIDA. ^{99m}Tc-HIDA was predominantly trapped by the liver via systemic circulation and is excreted into the gastrointestinal tract, through which it passes into the amniotic fluid[24].

Study III

An experimental study was performed for further confirmation of the meconium passage into the amniotic fluid by means of radionuclide techniques. Forty-eight New Zealand white rabbit fetuses at 25 days' gestation (fullterm = 31 to 32 days) were divided into two groups as A (n: 24) and B (n: 24). Technetium-99m (^{99m}Tc)-HIDA (0.1 ml) containing 1 mCi of radioactivity was injected into the gluteus muscle of each fetus which had been exposed through the uterus. Surgical closure of anus by a purse-string suture was performed in Group B.

After replacing the fetus and uterus into the abdomen, and beginning one hour after injection, a live fetus was sacrificed each hour for 24 hours in both groups. Tissue samples from the lung, heart, stomach, kidney, bladder and liver; meconium in the proximal, mid and distal bowel; and amniotic fluid were taken. The radioactivity of each sample was determined by a gamma counter and the percentage injected dose (uptake) per gram of tissue (%ID/g) was calculated. ^{99m}Tc-HIDA was predominantly trapped by the liver via systemic circulation and excreted into the gastrointestinal tract in both groups, through which it passed into the amniotic fluid only in Group A. The very low radioactivity levels detected in the amniotic fluid of Group B came from the urinary tract and indicated the in vivo stability of ^{99m}Tc-HIDA[25].

The result of the first study revealed that goat fetuses pass the contrast medium into the amniotic cavity in the absence of fetal distress with normal central venous blood gas values. This finding suggests that in utero defecation is independent from fetal distress. In the second study, we have clearly demonstrated for the first time the transport of radioactive meconium through the gastrointestinal tract into the amniotic fluid. Demonstrated passage of an excreted radiopharmaceutical agent through the fetal liver into the gastrointestinal tract and amniotic fluid, respectively, suggests that fetal defecation is a physiologic event. The result of the third study strongly supports the physiologic intestinal passage of meconium into the amniotic fluid, in other words in utero defecation.

Apart from our studies, the literature consists of evidence related to physiologic in utero defecation. The presence of anal meconium has been interpreted as positive proof of intrauterine defecation. Fetal defecation was considered to be a routine physiologic event through the second trimester until anal sphincter innervation is completed[7]. The concept of fetal defecation in early and mid-pregnancy was strengthened by the findings of high levels of both disaccharidases and intestinal alkaline phosphates (both specific to the fetal gut) in amniotic fluid during pregnancy[26,27]. Fetal defecation in early and mid-pregnancy can explain high amniotic fluid bilirubin levels, which peak at 17 weeks, plateau, and then gently fall as gestation proceeds. Presence of fetal defecation can be postulated in many cases of Rh-negative (and thus unaffected)

infants who have shown low but definite levels of bilirubin in amniotic fluid following amniocentesis in an Rh-negative woman with antibodies[7]. As much as 10 to 20 percent of total amniotic fluid protein comes from the fetal gut, suggesting that the mode of entry into the amniotic sac may be by fetal defecation[15]. The observation of numerous meconium pigment laden macrophages in the membranes of a placenta without gross staining suggested the possibility of silent intrauterine defecation with subsequent clearance of meconium from the amniotic fluid by fetal swallowing and/or macrophage uptake[28]. Defecation into the amniotic sac and subsequent meconiophagy were observed as normal occurrences in guinea pigs in experimental studies[29].

Prenatal detection of anorectal atresia is also considered evidence of fetal defecation[30]. Dilated bowel seen on prenatal sonography may be due to retention of meconium which normally passes into the amniotic cavity. Lastly, various conditions that specifically induce exaggerated fetal intestinal peristalsis, such as abortion by means of prostaglandins or fetal drug withdrawal, are associated with meconium passage even in the very premature human fetus without distress. This finding indicates that intestinal peristalsis plays the major role in the passage of meconium[6].

The second part of our hypothesis is mainly based on the clearance mechanism of the amniotic fluid. Continuity of the fetal gut lumen with the amniotic cavity is achieved when the buccopharyngeal membrane ruptures during the third week and the cloacal membrane during the seventh, establishing free circulation of amniotic fluid through the gastrointestinal tract[1].

Amniotic fluid plays an important role in gastrointestinal tract development[31] and nutrition of the fetus[32]. Amniotic fluid contains a range of physiologically active macromolecules. Receptors for epidermal growth factor, present in amniotic fluid, have been identified on fetal enterocytes at as early as 12 weeks' gestation[1]. This growth factor is believed to play a major role in intrauterine gastrointestinal development. The presence of fetal enzymatic activities in the amniotic fluid reveals the passage of meconium into the amniotic fluid.

Amniotic fluid provides 10 to 14 percent of the nutritional requirements of the fetus[32]. Long-term total parenteral nutrition results in degenerative changes of intestinal mucosa in adults. Enteral nutrition should be commenced to prevent these atrophic changes. The fetus lives in a total parenteral nutrition environment. Enteral nutrition provided by fetal swallowing is just as important in ensuring normal gastrointestinal homeostasis and growth in the fetus as it is in the adult receiving long-term total parenteral nutrition.

Recent studies have revealed that ingested amniotic fluid protein undergoes proteolysis in the fetal alimentary tract and the amino acids thus made available are utilized in protein synthesis by the fetus[34]. Additionally, intraamniotic galactose

infusion causes not only up-regulation of its own mucosal transport but also that of glucose along the entire fetal small intestine[35]. These findings reveal that the use of intraamniotic nutrition as a mode of fetal therapy, while speculative at present, offers possibilities for the future.

Apart from nutritive characteristics, amniotic fluid was found to contain fibronectin[36], and surfactant proteins A and D[37]. The presence of these proteins raises the possibility that amniotic fluid also has a role in the antibody-independent recognition and clearance of pathogens.

Amniotic fluid represents a dynamic fetal compartment and its turnover rate is very high. The volume increases from 20 to 30 ml at ten weeks to 800 ml at 30 weeks. The human fetus exchanges the amniotic volume totally by urinating, swallowing and respiratory tract secretions every 24-48 hours in the last trimester[24]. Fetal urine becomes the chief source of amniotic fluid and its ingestion the most important route for its elimination. This exchange caused by fluid dynamics, fetus and amniotic cells form the effective clearance mechanism of the amniotic fluid.

Fetal swallowing is the principal route of the clearance mechanism and the volume of swallowed amniotic fluid varies directly with the amniotic fluid volume. What biochemical or physical stimulus exhorts the fetus to vary its swallowing activity is not known, but this mechanism serves to stabilize the amniotic fluid volume and plays a major role in the clearance mechanism[1, 19]. It is shown that fetal swallowing, in other words the clearance mechanism of the amniotic fluid, is supressed in fetal distress conditions[5, 24]. Fetuses suffering from maternal distress are not able to normally release the intestinal content into the amniotic cavity[38]. Thus, we suggest that meconium-stained amniotic fluid is not related to meconium passage after fetal distress; rather, it reflects impaired clearance of amniotic fluid containing meconium caused by in utero defecation.

Meconium staining of the placental membranes and umbilical cord is a surface phenomenon and is proportional to both meconium concentration and the period of exposure. There is a critical difference between the presence of meconium in the amniotic fluid and meconium staining[22]. Evidence available from in vivo and in vitro observations suggests that a minimum of four to six hours is required between passage of meconium into the amniotic fluid and staining[28]. During this time, meconium is picked up by macrophages and simultaneously transported into the placental plate with fetal swallowing of the amniotic fluid[39]. Both of these mechanisms work to clear amniotic fluid from meconium under normal circumstances. However, under fetal distress, the clearance mechanism is impaired and thus meconium is stained.

Meconium-stained amniotic fluid causes amniotic epithelial destruction and vascular damage[39]. It also produces umbilical vein contraction[40] resulting in fetal hypoperfusion and distress. Both of these factors aggravate the impaired clearance of amniotic fluid and result in a vicious cycle in intrauterine life (Fig. 1).

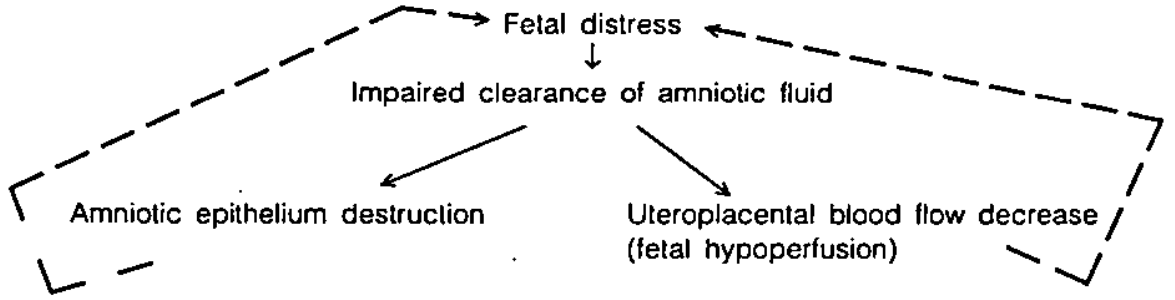

Fig. 1: Vicious cycle revealing the relation between fetal distress and amniotic fluid dynamics.

Our hypothesis also has many implications in various pediatric surgical fields which have until now been obscure[41, 42]. Chemical damage to the bowel in gastrochisis and to the spinal cord in myelomeningocele was accepted to be caused by fetal urine. Urinary ascites is a common symptom in newborns with obstructive uropathy. However, these patients do not present the signs or symptoms of chemical bowel damage such as intestinal dysfunction, peritonitis or morphological abnormalities. On the other hand, patients with meconium peritonitis show a diffuse chemical peritonitis induced by the various contents of meconium. On the basis of these findings, it appears more likely that the chemical damage of a primarily normal bowel or spinal cord is not related to urine content, but rather to the passage of meconium or, in other words, in utero defecation.

In light of our studies and the evidence in the literature, we suggest that in utero defecation is a physiological entity independent from fetal distress. Experimental studies on the clearance mechanism of the amniotic fluid is currently under evaluation in our research unit.

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