



Biochemical Markers in Meconium Passage

Mekonyum Salınımında Biyokimyasal Belirteçler

Mekonyumda Belirteçler / Markers in Meconium Passage

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Özet

İntrauterin mekonyum salınımının mekanizması ve patofizyolojisinin anlaşılması halen sınırlı kalmıştır. Yenidoğanda solumun yetersizliği ve mekonyum aspirasyon pnömonisine neden olması açısından mekonyum salınımı, doğumda istenmeyen bir durumdur. Sebebi net olarak bilinemediğinden, predikte etmek ve engellemek mümkün değildir.

Bu derlemede, mekonyum salınımında öne sürülen en son mekanizmalar ele alınmaya çalışıldı. Muhtemel patolojik mekanizmalar temel alınarak, potansiyel belirteçlerin tanıdaki yeri anlaşılmaya çalışıldı.

Anahtar Kelimeler

Mekonyum, Biyokimyasal Belirteçler

Abstract

The understanding of the mechanism and pathophysiology pertaining to intrauterine release of meconium is limited. An undesired condition of delivery, meconium passage can lead to respiratory difficulty and meconium aspiration syndrome. Since its mechanism has not been fully revealed, early prediction and prevention is not possible.

In this review article, an effort is made to gather the most current information on the mechanism of meconium release. Also, based on the probable pathologic mechanisms, an explanation is provided on the potential markers that can aid in early detection of meconium passage.

Keywords

Meconium; Biochemical Markers

DOI: 10.4328/JCAM.890 Received: 05.01.2012 Accepted: 17.01.2012 Printed: 01.03.2013 J Clin Anal Med 2013;4(2): 164-7
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Introduction

Meconium stained amniotic fluid is seen as a result of release of material by the fetal colon into the amniotic fluid. The prevalence of meconium passage into the amniotic fluid is 19 %; however, this condition is rare in preterm pregnancies and is more usually detected in pregnancies at and over 37 weeks [1, 2]. Meconium in the amniotic fluid can be found in 16.5 % of term pregnancies, while the incidence of meconium passage can be as high as 27.1% in post-term pregnancies [3, 4].

Pathophysiology Of Meconium Release

The understanding of the mechanism and pathophysiology pertaining to intrauterine release of meconium is limited. There are theories that are proposed to explain the passage of meconium. One is the maturation theory, linking fetal colonic maturation with meconium release. As the gestational age increases, the fetus matures and the fetal gut further develops. Regular contractions are seen in the fetal colon when maturation is complete or near-complete. These contractions, caused by cholinergic stimulation following the release of the hormone, motilin, are in fact an end result of fetal maturation and do not represent a pathologic process. According to this theory, the expulsion of meconium into the amniotic fluid with peristaltic movements is a consequence of a physiologic process involving the mature fetal colon.

The other theory, which is based on the concept of hypoxic stress, has received wider recognition and is the basis for many ongoing research projects involving human and animal subjects. At the time of delivery, fetal intrauterine hypoxia may induce stress hormones and increase fetal intestinal motility, cause relaxation of the rectal muscles and subsequent release of meconium [1,2,5-7].

Related with the other likely etiological factors for meconium release, intrauterine infection and gestational cholelithiasis were also pronounced [8]. The relation between maternal *Listeria monocytogenes* infection and meconium release has been known for a long time [9]. Intra-amniotic infection was demonstrated together with the clinical and histological chorioamnionitis in the neonates with meconium passage [10,11]. Prophylactic antibiotic administration in cases of meconium leakage was gone with a decreased risk of clinical chorioamnionitis which had revealed the increased rate of ascending intrauterine infection in meconium passage [12].

Gestational cholelithiasis has been associated with an increased risk of meconium passage [8]. Increased stillbirth rate in this disorder correlates with an increased rate of meconium stained amniotic fluid [13]. The probability of the meconium passage was related with the increased maternal bile acid levels which was also demonstrated in animal models of increased bile acid levels going together with in utero meconium release [14,15].

Reduced clearance of defecated meconium is another likely etiologic factor in meconium passage. Hypoxia induced meconium existence in the amniotic fluid is cleared by the fetus in most of the times but if any reduction in this clearance causes the meconium to accumulate [16].

Despite the extensive research on meconium passage the pathologic process for intrauterine release of meconium has not been fully elucidated [2]. In the current review, we aimed to gather up to date information on mechanisms of meconium release in association with certain molecular markers.

Potential Markers And Meconium Release

Corticotropin Releasing Factor

Corticotropin Releasing Factor (CRF), a stress hormone that is seen to rise acutely in response to stress, functions together with urocortin [17]. After binding to various receptors in the gastrointestinal tract, both hormones act to control motility [18]. By stimulating the cholinergic system and increasing colonic motility, CRF receptor 1 (CRF R1), a CRF-specific receptor subtype, is thought to be responsible for stress-induced dyspepsia and other complaints related to the gastrointestinal system [19,20].

Lakshmanan et al., studied the relationship between hypoxia and CRF with experiments conducted on mice [2]. In one such experiment, meconium was found in the amniotic fluid of fetal mice exposed to intrauterine hypoxia, whereas no meconium was detected in fetal mice in control groups that were not hypoxic [6]. Maternal and fetal blood levels of CRF were found to be significantly elevated at the end of the experiment. This finding has demonstrated that acute intrauterine hypoxia, by triggering the sympathetic nervous system and inducing the release of CRF, causes an increase in colonic motility and consequent release of meconium. A similar study showed the expression of CRF in endocrine cells in the colon of fetal mice and locally acting CRF is thought to have effects on intestinal motility [20,21].

Erythropoietin

Erythropoietin (EPO) is a growth factor that promotes cell formation. Tissue hypoxia and reduction in renal perfusion leads to hypoxia-induced renal secretion of the hormone [22-24]. Owing to its high molecular weight, EPO cannot cross the placenta. Therefore, maternal and fetal measurements are entirely unrelated, independently reflecting the plasma level of origin [25]. For this reason, EPO levels elevated in response to hypoxia can serve as an indicator of fetal hypoxia.

Richey et al., showed increased EPO levels associated with meconium release [26]. The study has received criticism due to a lack of gestational age-matched control groups and has fell short of determining EPO levels associated with passage of meconium. Consequently,

Jazayeri et al., once again studied EPO and demonstrated a significant relationship between elevation of EPO levels and meconium release [27]. The common basis for both studies has been the presumption of intrauterine hypoxia in the etiology of passage of meconium. Although, cord blood pH failed to objectively reveal the presence of hypoxia, high EPO levels suggest that a hypoxic environment exists in the setting of meconium release. Based on this relationship, EPO can be used as an indicator of intrauterine meconium release.

Under hypoxic conditions, EPO stimulates erythropoiesis and increases the supply of red blood cells, many of which are nucleated red blood cells (NRBC) in circulating blood [28]. After speculating that hypoxia can cause intrauterine passage of meconium, Darhaneh et al., found NRBC to be higher in newborns with intrauterine meconium passage. They explained their findings by the elevation of EPO secondary to hypoxia and the subsequent increase in NRBC [29].

Proinflammatory cytokines and chemokines

Proinflammatory cytokines and chemokines are chemical responders to various inflammatory and infectious conditions. These are other related chemicals studied in meconium passage. IL-1 β , IL-6, tumor necrosis factor (TNF)- α , and IL-8 were

isolated in the meconium and was blamed to be one of the responsible factors for the pneumonitis in meconium aspiration syndrome [30]. Meconium when added to the blood of normal donors in vivo had revealed increased levels of proinflammatory cytokines (TNF- α , IL-1 β , IL-6, IFN- γ), anti-inflammatory cytokines (IL-10, IL-1Ra) and chemokines (IL-8, MCP-1, MIP-1alpha, MIP-1beta, eotaxin, IP-10) [31]. In an alveolar cell culture media, meconium stimulated the cells in the way of increased production of IL-8 and TNF γ [30].

Meconium is a source of pro-inflammatory substances and can induce cytokine production in cultured A549 epithelial cells [30]. IL-1 and its receptor antagonist IL-1ra were evaluated in chorioamniotic and meconium stained placentas and were shown to be intense [32].

Other Indicators

Other indicators, studied less commonly, related to the intrauterine passage of meconium are summarized in Table 1.

Table 1. Biochemical markers in cord blood of neonates with meconium stained amniotic fluid.

Corticotropin Releasing Factor (CRF)
Erythropoietin (EPO)
IL-1 β , IL-6, tumor necrosis factor (TNF)- α
IL-8, MCP-1, MIP-1alpha, MIP-1beta, eotaxin, IP-10
C-reactive protein (CRP)
Vascular endothelial growth factor (VEGF)
Thrombin activatable fibrinolysis inhibitor activity (TAFIa)
IgE
Lactate: creatinine ratio
Endothelin (ET-1)
8-iso-prostaglandin F2 α
Asymmetric dimethylarginine (ADMA)

Silva-Bravo et al., investigated the role of inflammatory mediators, IL-6 and CRP in blood samples of newborns with meconium stained amniotic fluid. Their results revealed that meconium release was related to higher levels of IL-6. CRP levels, which were explored in conjunction with IL-6, were not shown to have a meaningful connection with meconium passage [33]. One similar study by Redzko et al. did not confirm any connection between blood levels of IL-6 and meconium release [34]. Vascular endothelial growth factor (VEGF) is another substance studied in association with meconium release. Research conducted by Teksam et al. did not demonstrate any significant differences in the levels of VEGF of newborns with meconium containing amniotic fluid when compared to newborns without passage of meconium [35]. Accordingly, they concluded that VEGF measurements cannot be used to predict the passage of meconium or the fetal distress that may follow the release of meconium. Another study [35] explored the role of Thrombin Activatable Fibrinolysis Inhibitor activity (TAFIa) levels in newborns with intrauterine meconium release [36]. This substance is a pro-inflammatory mediator also known to inhibit fibrinolysis. The authors assumed that the release of meconium is possibly a consequence of an inflammatory reaction or that hypoxia associated with meconium release leads to an inflammatory reaction. Indeed, the levels of TAFIa

were significantly elevated in newborns with meconium stained amniotic fluid. The investigators proposed that during the neonatal period, these newborns would likely suffer from additional hematologic disorders due to the inhibition of fibrinolysis.

Another study explored the concentration of Ig E in cord blood in newborns with intrauterine meconium release [37]. Higher blood Ig E levels were detected in newborns whose amniotic fluid contained meconium. The levels also appeared to be correlated with the degree of meconium release. Newborns with thick meconium stained amniotic fluid had higher levels of Ig E, when compared to those newborns whose amniotic fluid contained lighter meconium. The same study also demonstrated higher Ig E levels in newborns with meconium stained amniotic fluid in the presence of premature rupture of membranes.

Lactate: creatinine ratio, is another indicator, being explored in newborns with meconium release [38]. Lactate levels have been found to be higher in newborns with meconium stained amniotic fluid and especially in those with thick meconium in comparison to newborns with out meconium release. The same study demonstrated lower creatinine levels in the presence of meconium passage. Hence, a lactate: creatinine ratio higher than 0.13, an average value observed in newborns without meconium release, can serve as a threshold for meconium release and can be used as an early indicator.

Gemelli et al., studied the levels of endothelin-1 (ET-1) in cord blood of newborns with meconium release [39]. They postulated that hypoxia, commonly considered to be involved in the pathophysiology of meconium expulsion, would result in endothelial damage and subsequently raise levels of ET-1, one of the mediators released from the endothelium. Their research did not demonstrate any relationship between ET-1 and meconium release.

8-iso-prostaglandin F2 α is a lipid peroxidation marker that is a product of the oxidative stress in free radical reactions. Increased levels of this chemical is a sign of cell damage [40]. Liu et al., used this substance to explore oxidative stress in blood of newborns

with meconium release. The results demonstrated elevation of 8-iso-prostaglandin F2 α levels in meconium release and showed that these newborns were exposed to oxidative stress [41].

Asymmetric dimethylarginine (ADMA), is an endogenous competitive inhibitor of nitric oxide synthase and has some functions in the vasculature. Related with the pregnancy, ADMA levels increased in the newborn serum with meconium stained amniotic fluid who developed meconium aspiration syndrome [42]. This relation was based on the likely hypoxic conditions in meconium passage so that decreased blood flow to fetal kidneys during in utero hypoxia impaired ADMA excretion.

Conclusion

Meconium passage into the amniotic fluids is relatively common in term pregnancies. Its pathophysiology is not clear, and it can be an indicator of fetal hypoxia especially when accompanied by fetal distress. Since the exact mechanism has not been completely elucidated, early prediction and prevention of related morbidity may not be possible. Certain biochemical markers can aid in revealing the underlying disorder in meconium release. However, there is currently no marker that can be used for screening.

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