

Biochemical Markers in Meconium Passage

Mekonyum Salınımında Biyokimyasal Belirteçler

Mekonyumda Belirteçler / Markers in Meconium Passage

Ozlem Gun Eryilmaz, Esma Sarikaya, Serra Akar
Zekai Tahir Burak Women Education and Research Hospital, Turkey

Özet

İnrauterin 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): 162-165
Corresponding Author: Özlem Gün Eryilmaz, Zekai Tahir Burak Women Education and Research Hospital, Ankara, Turkey.
T.: 90 312 3103100 F.: 90 312 3096880 E-Mail: drozlemgun@yahoo.com

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 monocytogeneses 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]. Prophlactic antibiotic administration in cases of meconium leakage was gone with a decresaed 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-1β, 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-1β, 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-1β, 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 F2α
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 Redźko 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 teh 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 susbstance 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 F2α 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 at al., used this substance to explore oxidative stress in blood of newborns

with meconium release. The results demonstrated elevation of 8-iso-prostaglandin F2a 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.

References

1. Wiswell TE, Tuggle JM, Turner BS. Meconium aspiration syndrome: have we made a difference? Pediatrics 1990;85:715–21.
2. Lakshmanan J, Ross MG. Mechanism(s) of in utero meconium passage. Journal of Perinatology 2008;28:S8–S13.
3. Balchin I, Whittaker JC, Lamont RF, Ster PJ. Maternal and fetal characteristics associated with maconium-stained amniotic fluid. Obstet Gynecol 2011;117(4):828-35.
4. Oyelese Y, Culin A, Ananth CV, Kaminsky LM, Vintzileos A, Smulian JC. 2006 Meconium stained amniotic fluid across gestation and neonatal acid-base status. Obstet Gynecol; 108:345-49.
5. Walsh MC, Fanaroff JM. Meconium stained fluid: Approach to the mother and the baby. Clin Perinatol 2007;34:653-65.
6. Lakshmanan J, Ahanya SN, Rehan V, Oyachi N, Ross MG. Elevated plasma corticotropin release factor levels and in utero meconium passage. Pediatr Res 2007;61:176-79.
7. Berkus MD, Langer O, Samueloff A, Xenakis EM, Field NT, Ridgway LE. Meconium-stained amniotic fluid: increased risk for adverse neonatal outcome. Obstet Gynecol 1994;84(1):115-20.
8. Poggi SH, Ghidini A. Pathophysiology of meconium passage into the amniotic fluid. Early Human Development 2009;85:607–10.
9. Mazor M, Froimovich M, Lazer S, Maymom E, Glerzerman M. Listeria monocytogens. The role of transabdominal amniocentesis in febrile patients with preterm labor. Arch Gynecol Obstet 1992;252:109–12.
10. Kaspar HG, Abu-Musa A, Hannoun A, Seoud M, Shammas M, Usta I, Khalil A. The
placenta in meconium staining: lesions and early neonatal outcome. Clin Exp Obstet Gynecol. 2000;27(1):63-6.
11. Tran SH, Caughey AB, Musci TJ. Meconium-stained amniotic fluid is associated with puerperal infections. Am J Obstet Gynecol 2003;189:746–50.
12. Adair CD, Ernest JM, Sanchez-Ramos L, Burrus DR, Boles ML, Veille JC. Meconiumstained amniotic fluid-associated infectious morbidity: a randomized, double-blind trial of ampicillin-sulbactam prophylaxis. Obstet Gynecol 1996;88:216–20
13. Alsulyman OM, Ouzounian JG, Ames-Cstro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: perinatal outcome with expectant management. Am J Obstet Gynecol 1996;175:957–60
14. GlantzA,MarschallHU,Mattsson LA. Intrahepatic cholestasis of pregnancy: relationship between bile acid levels and fetal complication rates. Hepatology 2004;40:467–74.
15. Campos GA, Guerra FA, Israel EJ. Effects of cholic acid infusion in fetal lambs. Acta
Obstet Gynecol Scand 1986;65:23–6.
16. Yurdakök M. Meconium aspiration syndrome: do we know? Turk J Pediatr 2011; 53;121-29.
17. Tache Y, Martinez V, Million M, Rivier J. Corticotropin-releasing factor and the braingut motor response to stress. Can J Gastroenterol 1999; 13(Suppl A): 18A–25A.
18. Maillot C, Million M, Wei JY, Gauthier A, Tache Y. Peripheral corticotropin-releasing
factor and stress-stimulated colonic motor activity involve type 1 receptor in rats. Gastroenterology 2000; 119: 1569–79.
19. Hillhouse EW, Grammatopoulos DK. The molecular mechanisms underlying the regulation of the biological activity of corticotropin-releasing hormone receptors: implications for physiology and pathophysiology. Endocr Rev 2006; 27: 260–86.
20. Lakshmanan J, Richard JD, Liu GL, Ross MG. Corticotrophin releasing factor is a fetal gut hormone. Neurogastroenterol Motil 2008;20(12):1328-39.
21. Kawahito Y, Sano H, Kawata M, Yuri K, Mukai S, Yamamura Y, et al. Local secretion of corticotropin-releasing hormone by enterochromaffin cells in human colon. Gastroenterology 1994;106:859–65.
22. Jelkmann W. Erythropoietin:structure, control of production and function. Physiol Rev 1992;72:449-89.
23. Teramo KA, Widness JA. Increased fetal plasma and amniotic fluid erythropoietin concentrations: markers of intrauterine hypoxia. Neonatology 2009;95(2):105.
24. Kitanaka T, Alonso JG, Gilbert RD, Siu BL, Clemons GK, Longo LD. Fetal responses to long term hypoxemia in sheep. Am J Pysiol 1989;256:1348-54.
25. Reisenberg K, Egarter C, Kapiotis S, Sternberger B, Gregor H, Husslein P. Transfer of erythropoietin across the placenta perfused in vitro. Obstet Gynecol 1997;89(5 P 1):738-42.
26. Richey SD, Ramin SM, Bawdon RE, et al. Markers of acute and chronic asphxia in infants with meconium-stained amniotic fluid. Am J Obstet Gynecol 1995;172:1212-15.
27. Jazayeri A, Politz L, Tsibris JC, Queen T, Spellacy WM. Fetal erythropoietin levels in pregnancies complicated by meconium passage:does meconium suggest fetal hypoxia? Am J Obstet Gynecol 2000;183:188-90.
28. Hermansen MC. Nucleated red blood cells in the fetus and newborn. Arch Dis Child Fetal Neonatal Ed 2001;84:F211–F215.
29. Darkhaneh RJ, Asgharnia M, Yousef TZ. Comparison of NRBC in Term Neonatal Umbilical Cord Blood Between Neonate with Meconium-Stained Amniotic Fluid (MSAF) and Clear Amniotic Fluid. J Turkish-German Gynecol Assoc 2008;9(2):29-31.
30. de Beaufort AJ, Bakker AC, van Tol MJ, Poorthuis BJ, Schrama AJ, Berger HM. Meconium is a source of pro-inflammatory substances and can induce cytokine production in cultured A549 epithelial cells. Pediatr Res. 2003;54(4):491–95.
31. Salvesen B, Stenvik J, Rossetti C, Saugstad OD, Espevik T, Mollnes TE Meconium-induced release of cytokines is mediated by the TRL4/MD-2 complex in a CD14-dependent manner. Mol Immunol. 2010;47(6):1226-34.
32. Baergen R, Benirschke K, Ulich TR. Cytokine expression in the placenta. The role of interleukin 1 and interleukin 1 receptor antagonist expression in chorioamnionitis and parturition. Arch Pathol Lab Med. 1994;118(1):52-5.
33. Silva-Bravo R, Mayoral-Andrade G, Zenteno E, Hernandez P, Martínez-Cruz R, Mayoral LP, et al. Color of Meconium and Interleukin-6. Indian J Pediatr. 2011 May 28. [Epub ahead of print].
34. Redźko S, Przepieść J, Zelazowska B, Zak J, Wysocka J, Urban J. Ginekol Pol. Inflammatory mediators and hematological parameters in cord blood in labor complicated by meconium-stained amniotic fluid].2006;77(9):684-90.
35. Teksam O, Tekinalp G, Yurdakok M, Yigit S, Korkmaz A, Guc D. Indian J Pediatr. Vascular endothelial growth factor levels in newborns with meconium stained amniotic fluid. 2008 Oct;75(10):1015-7. Epub 2008 Sep 22.
36. Gursoy T, Tekinalp G, Yigit S, Kirazli S, Korkmaz A, Gurgey A Thrombin activatable fibrinolysis inhibitor activity (TAFIa) levels in neonates with meconium-stained amniotic fluid. J Matern Fetal Neonatal Med 2008 Feb;21(2):123-8.
37. Song F, Zhou XS, Wang T, Jin T, Peng QY. IgE level of cord blood in neonates with meconium-stained amniotic fluid. Zhongguo Dang Dai Er Ke Za Zhi. 2007 Aug;9(4):361-3, Abstract.
38. Ojha RK, Singh SK, Batra S, Sreenivas V, Puliyel JM. Lactate: creatinine ratio in babies with thin meconium staining of amniotic fluid. BMC Pediatrics 2006, 6:13.
39. Gemelli M, Manganaro R, Mamì C, Buemi M, Paolata A, Marrone T, et al. Endothelin-1 concentrations in cord blood of neonates with meconium-stained amniotic fluid. J Perinat Med. 2005;33(3):259-61.
40. Montuschi P, Barnes P, Roberts LJ. Insights into oxidative stress: the isoprostanes. Curr Med Chem 2007;14:703-17.
41. Liu BY, Wang CC, Lau TK, Chu CY, Phil M, Pang CP, Rogers MS, Leung TN. Meconium-stained liquor during labor is associated with raised neonatal cord blood 8-iso-prostaglandin F2alpha concentration.Am J Obstet Gynecol. 2005;192(1):289-94.
42. Kul M, Demirkaya E, İpçioğlu OM, Karadeniz RS, Tunç T, Vurucu S, Yeşil FG, Öztin H, Çakır E. Perinatal risk factors affecting the maternal and fetal asymmetric dimethylarginine levels. Turkish J Pediatr 2009;51:141-45.