Journal of Women's Health Care
ISSN: 2167-0420

Erez and Mazor, J Women's Health Care 2013, 2:1
DOI: 10.4172/2167-0420.1000e109

Editorial Open Access

The Role of Late Amniocentesis in the Management of Preterm Parturition

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Preterm labor and preterm PROM are both obstetrical syndromes leading to spontaneous preterm birth. This is one of the leading causes for maternal and neonatal morbidity and perinatal mortality [1-3]. Indeed, premature delivery has a lifelong effect on the neonates, ranging from severe morbidities near to the time of birth (i.e. respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis and sepsis) to chronic morbidities later on in life (i.e. retinopathy of prematurity, bronchopulmonary dysplasia, cerebral palsy, and reduces mental and cognitive functions) [1-3]. The Institute of Medicine in the USA has estimated in 2005 that the annual cost of these obstetrical syndromes is about 25 billion US Dollars [4]. Thus, there is urgent need for tools that will assist in prevention and treatment of prematurity.

The treatment modalities for preterm labor accustom today including tocolysis, corticosteroids, antibiotic, and in some cases cervical cerclage, are of limited benefit. Although, the combination of tocolytic agents along with corticosteroids for the acute episode of preterm parturition prolongs gestation by few days and reduces acute neonatal morbidity, they were not able to prevent preterm delivery. Moreover, the trials testing the implementation of cervical cerclage for the prevention of preterm birth in women with a short cervix yielded disappointing results [5]. While the administration of prophylactic antibiotic treatment for patients admitted with preterm labor did not prolong their pregnancy or improved the neonatal outcome [6]; and even worsen the long term outcome of these neonates, since a 7 years follow up showed that those treated with antibiotics had a higher rate of cerebral palsy and abnormal neurological development in comparison to the placebo group [6]. Therefore, the paradigm that a single treatment modality will be effective in all women with preterm parturition is no longer valid. The clinicians are left with a dilemma of how can we tailor an effective treatment for women with preterm parturition? [7]

Understanding the syndromic nature of preterm labor and preterm PROM is the key for a potent treatment to preterm parturition. Indeed, as much as we treat differently anemia that results from iron or vitamin B-12 deficiencies, the treatment of preterm labor resulting from infection/inflammation or from a placental vascular disease should be different [1-3]. This approach is relevant for both prevention and acute management of spontaneous preterm parturition. The first stepsin, a differential treatment for patients with preterm parturition are being done today with the administration of progesterone for the prevention of preterm birth and in women with a short cervix [8-11], as well as those with a history of preterm delivery [12]. Moreover, the placement of a cerclage has been found efficacious for the prevention of recurrent preterm birth in women with such history of a prior preterm birth and a short cervix at the mid trimester [13,14]. Nevertheless, these treatments reduces the rate of recurrent preterm birth in about 40-50% and are not suitable for the management of the acute event of preterm labor or preterm PROM.

Thus, the question at hand is how to craft an effective treatment for the acute episode of preterm parturition. In order to address that, we first have to take into account what are the diagnostic tools we have in order to identify the underlying mechanisms leading to preterm labor or preterm PROM. The efforts to identify markers in the maternal circulation or in sonographic examination that will ascertain these mechanisms (i.e. intrauterine infection/inflammation or maternal vascular disease) were not successful so far. A possible explanation is that apart from clinical chorioamnionitis most of the processes leading to preterm parturition are confined to the uterus. Thus, there is a need for an alternative diagnostic tool that will enable the clinician to properly asses the etiology of preterm labor or preterm PROM.

Amniocentesis can be a useful tool for the identification of the underlying mechanisms leading to preterm parturition. Today, we can obtain valuable information from a sample of amniotic fluid including all of the following: 1) intra-amniotic infection and or inflammation can be identified by direct vision of bacteria in a Gram stain [15-19], measurement of low amniotic fluid glucose (<15mg/dL) [20-23], elevated white blood cells count (>50 WBC's) [24-30], positive aerobic, anaerobic, as well as, genital mycoplasma cultures [31-35] and PCR for bacteria [36-38] and viruses [39], In addition, the measurement of cytokines (i.e. IL-6) and other markers of inflammation such as the rapid kit for the measurement of MMP-8 [40,41] are regarded as valid markers for infection and inflammation and for the development of fetal inflammatory response syndrome, 2) In the absence of intra-amniotic infection or inflammation vascular disease or increased thrombin generation can be identified by measuring the amniotic fluid concentration of thrombin ant-thrombin III complexes. Indeed, among women without intra-amniotic infection/inflammation, high amniotic fluid concentrations of this molecule were associated with a shorter amniocentesis to delivery interval and lower gestational age at delivery in comparison with normal or low concentrations of TAT III complexes [42], 3) The injection of indigocarmine allows us to verify the rupture of the membranes, 4) To test for fetal lung maturity and 5) To study fetal chromosomal abnormalities either by FISH or by cell culture. Collectively amniocentesis enables the clinician to detect the leading causes for preterm birth; moreover, the study of amniotic fluid may assist us to develop additional assays for other mechanisms of prematurity.

What is the safety of late amniocentesis? Many clinicians and patients express their concern regarding the safety of amniocentesis in women with preterm parturition. Although this question was not tested by a randomized clinical control trial, Gordon et al. [43] studied the rate of third trimester complications in 562 patients and the rate of

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Received December 04, 2012; **Accepted** December 06, 2012; **Published** December 09, 2012

Citation: Erez O, Mazor M (2013) The Role of Late Amniocentesis in the Management of Preterm Parturition. J Women's Health Care 2:e109. doi:10.4172/2167-0420.1000e109

complication was 0.7% while there was no need for emergency cesarean delivery and no perinatal mortality associated with late amniocentesis. Moreover, the complications were not associated with the number of needle sticks, presence of bloody fluid or level of operator experience. Hodor et al. [44] conducted a case control study regarding the risk of late amniocentesis in patients with pregnancy complications including preterm labor, hypertension, gestational diabetes and fetal growth restriction. The performance of amniocentesis was not associated with increased risk of urgent delivery, PROM, placental abruption, Apgar score at 5min<7 or perinatal death. In addition, Gabbay et al. [45] studied the outcome of 168 third trimester amniocentesis. Only one patient (0.6%) delivered by 48 hours after the procedure. The authors concluded that the risk for prematurity is low after third trimester amniocentesis.

Can late amniocentesis improve pregnancy outcome in patients with preterm parturition? Although this question was not studied in randomized controlled trial, there are reports indicating that the incorporation of amniocentesis in the management of preterm parturition improves pregnancy outcome. Indeed, antibiotic treatment in women with preterm labor or a short cervix, who had a positive amniotic fluid culture of indolent pathogens such as genital mycoplasmas, achieved eradication of these pathogens from the amniotic fluid and favorable pregnancy outcome [46-48]. Moreover, among patients presenting with preterm PROM those who had amniocentesis had a higher gestational age at delivery and better neonatal outcome [49]. Finally, a recent meta-analysis suggested a beneficial effect of repeated amnioinfusion in the management of preterm PROM [50].

In conclusion, the preliminary evidence brought herein support the rational of the performance of late amniocentesis as part of the workup of women with preterm parturition. This procedure may give the clinicians additional information and tools to decipher and understand the underlying mechanisms leading to these syndromes in a specific patient, and tailor their treatment accordingly.

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