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CHALLENGING UTERINE CERVICAL INCOMPETENCE MOLECULAR PATHOPHYSIOLOGY

Abstract

We present systemic analysis of publications dedicated to the challenging field of uterine cervical incompetence (UCI) molecular pathophysiology. 792 papers published between May 1974 and October 2013 were browsed to select and highlight key points of the contemporary understanding of UCI.

Introduction

Uterine cervical incompetence (UCI) is a type of pregnancy complications usually diagnosed in the second trimester and characterized by: passive painless cervical dilation in the absence of uterine contraction; bleeding; infection; and sometimes with the amniotic sac bulging through the partially dilated cervix. Left untreated, this condition may lead to premature pregnancy loss (according to the current MeSH term) [20]. UCI affects about 10% of pregnancies in the western world [22]. UCI is one of notorious highly heterogeneous pregnancy complications [22, 32]. To authors’ knowledge, no exact pathophysiological nor etiological molecular mechanisms of the UCI development have been proposed to date [23]. Ludmir and Sehdev comprehensively formulated the existing problem in the following words: “...the signals responsible for the initiation of these changes [cervical ripening] remain to be elucidated. If we can understand the exact mechanisms that affect these changes, then we may be better able to address such complex issues as cervical incompetence.” [19] Anatomical

features, infections, inflammation, genetic predisposition, abnormal implatation are proposed as risk factors [22, 32], though the basis for these speculations is not firm due to scarce experimental information. As even literature analysis is challenging in uterine cervical incompetence, we aimed at performing fast yet systemic analysis of papers addressing UCI in whatever aspect.

Methods

Paper search was performed in NCBI PubMed with “uterine cervical incompetence” request. Search details section confirmed term database and advanced search options had been engaged during query processing: we had “"uterine cervical incompetence"[MeSH Terms] OR ("uterine"[All Fields] AND "cervical"[All Fields] AND "incompetence"[All Fields]) OR "uterine cervical incompetence"[All Fields]” query syntax translation. “Abstract available” filter was further applied.

Results and discussion

The search yielded 792 papers with abstracts available. The most recent (by publication date) paper found had PMID 24170246, and the oldest paper found had PMID 4822660. Three major topics are concerned in the literature: relative efficiency of different types of cerclages and pessaries; cost-effectiveness of predictive approaches and preventive and emergency cerclages; general and molecular pathophysiology of UCI. As the first topic is out of the scope, we review here only the two last problems. 30 papers were analyzed based on topics considered.

Physiological features of UCI

Historically, UCI has been treated as pregnancy complication caused by anatomic defects and physiologic malfunctions of uterine cervix tissues.

Generally, two major groups of UCI were considered - those caused by connective tissue disorders and those caused by uterine cervix tissues lesions and malfunctions (adrenoreceptor dysfunction, hyperandrogenia, connective and muscular tissues imbalance) [29]. However, the molecular evidences for these UCI cases as well as for UCI variants emanating not from the disturbances of the uterine cervix tissues themselves are relatively recent. Moreover, the later group of UCI causes is poorly presented in the literature.

Warren et al. (2007) found that the COL1A1 intron 1SP1 and TGFB1 Arg-25-Pro polymorphisms are associated with the condition. These authors also analyzed families and revealed that over one fourth of women with cervical insufficiency had a family history of the syndrome [8]. Later, Anum and co-authors (2009) revealed that Marfan syndrome, caused by FBN1 mutations, and polymorphisms in the COL1A1 and TGFB1 genes are associated with UCI [9]. Thus, UCI appears to be considerably linked to collagenopathies and other connective tissue disorders.

In contrast to this common view seen also in other sources [24], Oxlund and colleagues (2010) showed that UCI does not appear to be associated with a constitutionally low collagen concentration or collagen of inferior mechanical quality. Furthermore, the hypothesis that a "muscular cervix" with an abundance of smooth muscle cells contributes to the development of cervical insufficiency was not supported by the study [7]. Moreover, Dudenhausen et al. (1987) showed that the concentration of elastase in the plasma of pregnant women is not affected by UCI [11].

Although the molecular basis of tissue-related causes of UCI remains unclear, generalized anatomic studies may be of value. From this point of view, House et al. (2012) suggested biomechanical modeling as a tool for studying the fundamental pathophysiology of cervix shortening in UCI [31].

The second, and the biggest part of the research projects dedicated to UCI dealt with immunologic aspects of the syndrome. The factors reviewed below, though methodologically opposite, have generally the same nature - the problem of organismal identity and intruders.

Mohapeloa and colleagues suggested that HLA-DR-associated immunological factors may play a role in extremely preterm births under a cervical incompetence-like picture, at least in cases not treatable by cervical cerclage [21]. Endres and Wang addressed the involvement of cytokine system in UCI several times. In 2003 they found that G-308A TNF polymorphism was not associated with cervical incompetence or with delivery prior to 28 weeks in women who received an emergent cerclage [13]. Later they tested expression of TNF and also IL6 in UCI. TNF was not increased in women with cervical incompetence and did not predict success of emergent cerclage. IL6 levels were increased in UCI patients requiring emergent cerclage compared with control subjects, but there were no differences between cerclage success and failure groups [12]. In agreement with data provided by Endres and Wang, Lee and co-authors (2004) found that amniotic fluid IL6 is increased in UCI patients. In contrast to IL6, amniotic fluid relaxin was suggested as a factor not contributing to cervical incompetence-induced cervical dilation (regarding relaxin levels consider that group sizes in the study were 40 and 45 women in UCI and control groups, respectively) [18]. Later, Warren et al. (2009) found that G13 allele in the interleukin-10.G microsatellite (promoter polymorphism) was more frequent in UCI women when compared to controls [25].

Aguin and colleagues (2012) showed that elevated amniotic fluid (AF) IL-6, elevated white blood cell count (WBC) and low AF glucose, in the absence of a positive AF culture, are significantly associated with adverse pregnancy outcomes in patients undergoing nonelective cerclage. Elevated

AF WBC correlated with severe and extreme preterm delivery; low AF glucose was associated with chorioamnionitis and decreased cerclage-to-delivery interval; elevated AF IL-6 was associated with decreased gestational age at delivery and decreased cerclage-to-delivery interval; higher IL-6 concentrations were associated with severe, extreme preterm delivery and neonatal death in UCI cases [2].

Steinborn and colleagues (2012) analyzed composition of the systemic regulatory T cell (Treg) pool in patients suffering from UCI and other pregnancy complications. The authors found that percentage of naive DR(-) CD45RA(+) T(regs) was reduced significantly in the presence of preterm labour necessitating preterm delivery (this group included patients with UCI) when compared to controls. PL was also accompanied by a significantly increased percentage of DR(-) CD45RA(-) and DR(low+) CD45RA(-) T(regs). The suppressive activity of the total T(reg) cell pool was diminished in the preterm labour group. Authors propose that preterm delivery is characterized by homeostatic changes in the composition of the total T(reg) pool with a significant decrease of Treg suppressive activity [26].

In opposite to studying immunological status of UCI patients, several research groups concentrated their effort on revealing microbiotic contributors of UCI.

Bakuma and co-authors (1990) demonstrated that in pregnant women with a pathologic swab, in spite of the cervical cerclage, spontaneous abortions and premature deliveries were significantly more frequent than in pregnant women with a sterile swab [3].

Romero and colleagues (1992) in the series of works showed that: (1) microbial invasion of the amniotic cavity occurs frequently in women presenting with cervical dilatation in the midtrimester; (2) the microbiologic state of the amniotic cavity is an important prognostic factor

for pregnancy outcome; (3) amniocentesis to determine the microbiologic characteristics of the amniotic cavity should be considered before a cerclage is placed in women presenting with cervical dilatation in the midtrimester [17].

Significantly later, Oh and colleagues (2010) also studied microbial status in UCI patients. The authors demonstrated that UCI patients with a negative amniotic fluid culture and a positive PCR assay (i.e. false-negatively culture tested) were at risk for intra-amniotic and fetal inflammation, and spontaneous preterm birth [10]. These data are in good agreement with those obtained earlier by Lee and co-authors [2008]: intraamniotic inflammation, regardless of AF culture result, was present in approximately 80% of patients with acute cervical insufficiency and was a risk factor for impending preterm delivery and adverse outcomes [30].

Kobayashi and co-authors (2011) demonstrated that in women with indicated cervical cerclage between 17 and 26 weeks of gestation, increased levels of serum C-reactive protein on post-cerclage day 1 or 2 might be ominous signs for very preterm birth [5].

Taking into account that pregnancy complications are often associated with oxidative status disturbances, our lab applied interactomics-based oxidative status probing approach [23]. We found that UCI is surprisingly associated with attenuated pro-oxidant systems' performance, possibly implying impaired pro-oxidant-dependent signaling events leading to development of UCI.

Cost-effectiveness of UCI prediction, prevention and emergent treatment

Classical diagnostics of UCI is based on immediate medical anatomic surveying. However, this group of methods is limited in timeliness and informativeness [29]. Thus, the measures for UCI prediction and prevention are widely discussed.

Illanes and colleagues (2011) tested whether plasma free fetal DNA (ffDNA) measurement at 22-24 weeks of gestation is helpful in predicting preterm labour in UCI patients. The authors state ffDNA measurement does not increase the accuracy of short cervix-based-only prediction of preterm labour when the test is performed at 22-24 weeks [16].

Another diagnostic study was performed by Benson et al. (2012). The authors demonstrated that cervicovaginal fetal fibronectin testing is a valid diagnostic tool in evaluation of preterm labor in cervical cerclage patients which has sensitivity of 100% and specificity of 77% [15].

In relation to pathophysiological heterogeneity of UCI, Sakai and co-authors provided evidences that tracheloplasty in the case of cervical shortening may reduce the rate of preterm delivery only when cervical mucus IL-8 at 20-24 weeks is within normal range (less than 360 ng/mL); cerclage in the setting of elevated cervical mucus IL-8 may be harmful [14]. Similar results were obtained by Weiner et al. (2005): intrauterine inflammatory response or decidual hemorrhage predate surgery in one half of the women requiring rescue cerclage. Activation of either mechanism predicts cerclage failure [27].

Hui et al. (2013) surveyed 4438 pregnant Chinese women. 4.6% (203 women) had a cervical length of less than 25 mm at 20 to 24 weeks' gestation, 108 of these women consented for randomized UCI-preventive cerclage pessary and control follow-ups. The prophylactic use of cerclage pessary did not reduce the rate of preterm delivery before 34 weeks [6].

Barth, Yeomans and Hankins shared their experience of emergent cerclages in UCI cases. During a five year period, 15 patients with bulging or hourglass membranes and marked cervical dilation in the second trimester were treated with emergent cerclage. Pregnancy was prolonged for a sufficient time to deliver viable fetuses in 11 of 15 patients. Eleven of 13 neonates of a gestational age of 24 weeks or more survived [4].

Conclusion

We would like to close this paper with two citations representing perfectly the trends in the UCI understanding and management seen from the review. We cite here papers by Althuisius and Dekker (2005), and Shortle and Jewelewicz (1989). “Since cervical incompetence was introduced in the English literature in 1678, our understanding and obstetric management of this clinical entity, have changed tremendously over the years” [1]. Shortle and Jewelewicz brought up the obverse in a very neat manner: “In the early 1950s, when treatment of cervical incompetence was first described, diagnosis seemed relatively simple and management favorable, but after more than 35 years of trying multiple variations of procedures and treatment regimens, no advances have been made. In 1959, Neser questioned the very existence of cervical incompetence as an entity, and concluded that, in the final analysis, the problem is a diagnostic one. Liberal use of cerclage in situations of moderate risk of preterm delivery or as a prophylactic measure for multiple gestation does not appear to improve outcome, as judged by prematurity or survival. Because of advances in neonatal care in the last decade, fetal survival has improved tremendously. It is hoped that, in the future, more objective and accurate criteria for the diagnosis of cervical incompetence will emerge, and that outcome of treatment will be measured not by fetal survival, but by prolongation of pregnancy and by birth weight. At present, making an unequivocal diagnosis of cervical incompetence remains an elusive, challenging, and unsolved problem [28]. The words written by Shortle and Jewelewicz 24 years ago seem to be fair thus far. One possible reason for the present situation may lie in a surprising lack of applying of novel advanced biomedical techniques available today towards UCI studying.

Conflict of interests

No competing financial or other interests exist.

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