

Efficacy of Candinet® Vaginal Tablets for the Prevention of Premature Rupture of Membrane and Preterm Labour in Pregnancy

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Abstract

Premature rupture of membrane (PROM) and preterm birth are the primary cause of infant morbidity and mortality in the world-wide. Bacterial vaginosis (BV) and Vulvovaginal candidiasis (VC) are the main risk factors for PROM and preterm birth. The purpose of this observational study was to evaluate the use of Candinet vaginal ovules in pregnant women with BV or VC during the third trimester in order to reduce infection, restore pH and prevent PROM and preterm labour. We recruited 70 pregnant patients and divided them into two groups. Thirty-five patients were treated with Candinet® vaginal tablets (one tablet twice a week from the 14th to the 36th week of pregnancy) (Group 1). The other 35 patients did not receive any therapy (Group 2). Our study demonstrated the efficacy of Candinet in reducing the risk of PROM and preterm labour, suggesting that it could be used to prevent and treat PROM, preterm delivery and its complications.

Keywords: Candinet®; Premature Rupture; Preterm Labour; Pregnancy

Introduction

The WHO defines preterm birth as any birth before 37 completed weeks of gestation [1]. Complications associated with prematurity are the leading cause of death in children under 5 years of age [2]. Survivors often suffer significant motor and sensory deficiency, learning and developmental disorders and respiratory disorders [3]. Premature rupture of membrane (PROM) occurs in about 8% of pregnant women worldwide, while the global average preterm birth rate in 2010 was 11.1%. PROM and preterm birth rate vary widely between countries, with higher rates in low-income countries (PROM 11.8%) and lower in high-income countries (PROM 9.3%) [4]. Nearly 40% of PROM and preterm births are associated with intrauterine infection caused by colonization of the vagina with pathogenic bacteria [5]. This activates an inflammatory cascade, leading to remodelling, demolition of the membrane structure and hence premature rupture [6]. Healthy pregnancy is characterized by a stable, low-richness bacterial population consisting predominantly of *Lactobacillus* spp. [7], essential to inhibit growth of pathogenic bacteria [8].

Bacterial vaginosis (BV) is the most common vaginal infection among women aged 14 - 49 years, with a prevalence of 22 - 50% [9]. It is a synergistic, polymicrobial infection characterized by a disturbance in the natural vaginal microbiota (reduction in lactobacilli) and an overgrowth of anaerobic bacteria. BV during pregnancy is the main risk factor for PROM and preterm birth [10].

Vulvovaginal candidiasis (VC) is estimated to be the second most common cause of vaginitis after BV, and is found in 40% of women with vaginal discomfort [11]. VC can cause systemic infections in premature neonates, particularly those with low birth weight [12]. Vaginal infections in the third trimester of pregnancy are also an important risk factor for PROM and preterm labour. Literature evidence

suggests that screening and eradication of BV and VC during pregnancy can reduce the risk of premature birth [13,14]. Early diagnosis is extremely important to identify women at risk and to resolve the infection as quickly as possible.

Pregnant women are more susceptible to vaginal infections due to both a diminished immune response and altered hormone production, determining an adverse vaginal environment favourable to bacterial reproduction. The detection of changes to the vaginal microbiota can be considered a marker of vaginal infection [15,16]. Restoration of the optimal vaginal pH is essential to fight such infections.

Candinet® vaginal ovules contain a type of bacteria called *Bacillus Coagulans* (BC). BC produces lactic acid and forms reproductive structures called spores which have acidifying properties [17]. Another component of these ovules is Sunfiber R, a galactomannan based soluble fiber made from hydrolyzed guar gum. Sunfiber is a prebiotic fiber that helps improve beneficial probiotics, not only in the bowel but also in the vaginal vault [18]. Candinet® ovules contain also Polycarbophil able to reduce vaginal pH. Polycarbophil, a weak polyacid, is a large molecule that it is able to stick on the vaginal epithelial cells until they turnover, up to 3 - 5 days, and buffers the vaginal secretions near its pKa (i.e. 4.3) [19]. All these ingredients help to restore the balance of the vaginal bacterial microflora, with prebiotics and probiotics to improve vaginal health by creating an environment less receptive to the proliferation of pathogens, helping maintain a healthy vaginal ecosystem. Candinet's ingredients help maintain the normal vaginal microbiota.

Purpose of the Study

The purpose of this observational study was to evaluate the use of Candinet vaginal ovules in pregnant women to prevent BV or VC during the third trimester in order to reduce infection, restore pH and prevent PROM and preterm labour.

Materials and Methods

We recruited 70 pregnant patients and divided them into in two groups. Thirty-five patients were treated with CANDINET® vaginal tablets (one tablet twice a week from the 14th to the 36th week of pregnancy) (Group 1). The other 35 patients did not receive any therapy (Group 2).

All patients tested negative on vaginal swab at the 14th week of pregnancy. All patients repeated the vaginal swab and underwent cervical length measurement by transvaginal ultrasound between the 24th and 30th week and between the 32nd and 36th week of pregnancy. Vaginal swab and cervical length measurements were repeated every time a patient reported an increase in leucorrhoea.

The exclusion criteria were: multiple pregnancy, previous preterm labour or previous PROM, cervical cerclage or Arabin pessary. Patients with positive vaginal swab were also excluded.

Results

The results are summarized in table 1.

	Candidiasis	Bacterial vaginosis	Prom	Vaginal delivery	Caesarean delivery	Preterm delivery
Group 1 (Candinet)	1	3	--	33 (94%)	2 (6%)	1 (3%)
Group 2 (No Therapy)	5	7	6 (17%)	30 (86%)	5 (14%)	6 (17%)

Table 1: Results of the study.

In Group 1 (patients treated with Candinet®), one patient (3%) developed Candida infection and three (8.5%) developed bacterial infections during the study period. No PROM occurred. Thirty-three patients (94%) delivered spontaneously, and two (6%) by caesarean section. There was only one case of preterm labour (3%).

In Group 2 (control patients), five patients (14%) developed Candida infections and 7 (29%) bacterial infections during the study period. Thirty patients delivered spontaneously (86%). Five patients (14%) delivered by caesarean section. There were six preterm labours (17%): of these, one was at week 34, two at week 36 and one at week 37. There were six cases of PROM (17%).

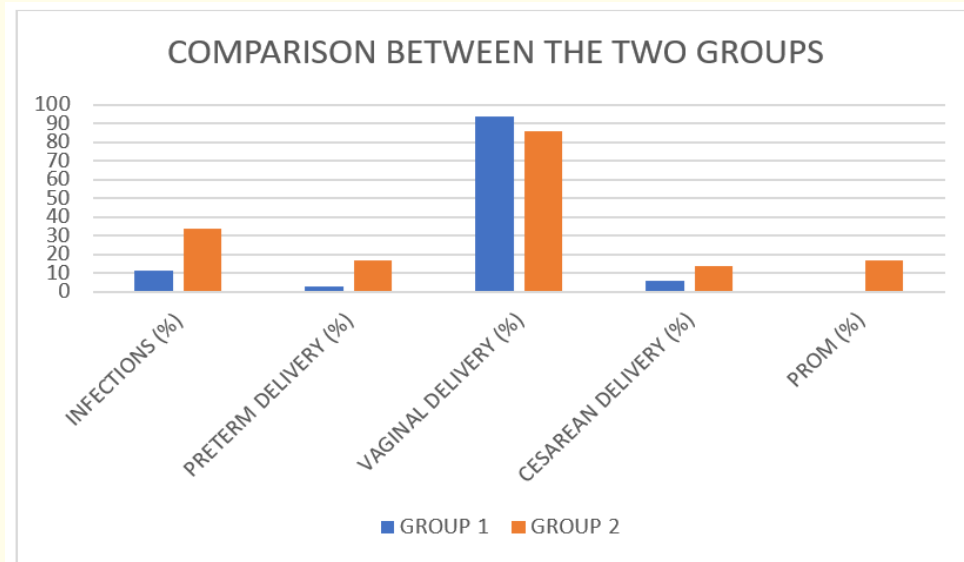


Figure 1: Comparison between the two groups.

Discussion

PROM, defined as rupture of the amniotic membranes before the 37th week of pregnancy, remains a serious challenge for gynaecologists due to the high rate of associated complications, above all preterm labour [3]. The aetiology of PROM is multifactorial, but there is a body of evidence to suggest an association between vaginal infection and increased risk of PROM [5-7]. Management of pregnant women with or at risk of PROM is still one of the most important issues in obstetric practice. Unfortunately, strategies for its prevention are somewhat controversial, given the inconsistent supporting evidence [20].

BV and VC are a major risk for pregnant women, as they can cause PROM and preterm labour. Adequate screening is essential for prompt identification of patients at risk and early intervention. The use of traditional acidifying vaginal preparations (douches, capsules, tablets) is generally limited by the transient nature of their pH-lowering activity [21]. Douches, capsules and pessaries for local use containing lactic acid have only a temporary effect because they are quickly absorbed and metabolized. Furthermore, douches can actually worsen the situation by removing vaginal mucus.

Bio-adhesive formulations are able to adhere to human mucosa (oral mucosa, vaginal mucosa, etc). Polycarbophil is one of the most bio-adhesive polymers known to date. When applied to the mucosa, it forms non-covalent bonds with the mucus secreted by the tissues (negative load), thus remaining *in situ* for prolonged times (more than 72 hours) [22]. From a chemical perspective, polycarbophil mimics mucin, which is secreted by the epithelial cells of the mucosa, forming a protective film. Once bound to the vaginal mucus, polycarbophil constantly releases H⁺ ions, which help lower the pH of the vaginal environment. It thus acts as an effective buffer, capable of “normalizing” an elevated vaginal pH [19]. The pKa of polycarbophil is 4.3, which is very similar to the natural pH of the vagina (pKa is the pH value at which a buffer solution begins releasing H⁺ ions). It is thus an ideal buffer for the vaginal environment. In contrast with all the traditional formulations used to acidify the vaginal environment, therefore, polycarbophil has two distinctive and unique properties: bio-adhesiveness and prolonged buffer effect [23,24].

Bacillus coagulans (BC) is a sporogenic bacterium that acidifies the environment by producing lactic acid. Its spores can survive and sporulate in a pH as low as that found in the stomach, let alone that of the vagina [17]. BC acts in synergy with polycarbophil: by mimicking the function and adhesive properties of mucus, polycarbophil prolongs the persistence of BC *in situ* as well as helping to restore the vagina's acidity. BC has been added by the European Food Safety Authority (EFSA) to the list of products with a qualified presumption of safety [25]. There is also considerable evidence of the safety of the use of BC in humans, especially when used to improve the vaginal flora [26].

Numerous authors have investigated the benefits of lactobacilli in the treatment of vaginal infections [27]. After insertion, the probiotics in Candinet Vaginal Ovules release millions of live probiotics. A major benefit of Candinet is that BC spores can survive in conditions in which many other probiotics would succumb. On the basis of the literature evidence [15,28], Candinet Vaginal Ovules can reasonably be used as a medical device for the maintenance of the vagina's physiological pH.

Conclusions

Our study demonstrated the efficacy of Candinet in reducing the risk of PROM and preterm labour, suggesting that it could be used to prevent and treat preterm delivery. In conclusion, Candinet is a valuable tool for the prevention of PROM and its complications. Multicentre randomized clinical trials are needed to standardize the preventive therapy of PROM and preterm labour.

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