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ORIGINAL ARTICLE

Infectious complications in morbidly adherent placenta treated with leaving placenta *in situ*: a cohort series and suggested approach*

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ABSTRACT

Background: The aim of this study is to assess the clinical and microbiological features of infections in patients with morbidly adherent placenta (MAP) treated by leaving placenta *in situ* (LPIS).

Materials and methods: Retrospective analysis of MAP cases who were treated by LPIS between 2 May 2010 and 15 March 2017. The inclusion criteria were gestational age at or above 24 weeks, prenatal diagnosis, elective operation, and complete data.

Results: Nineteen MAP cases were treated by LPIS during the study period. The mean ± SD duration for total placental resorbtion was 145 ± 47 days. Three patients were readmitted to the hospital because of fever (3/19). A total of 65 culture samples were taken from the patients during their follow- up periods. In four cases (4/12) cervical cultures showed positive growth [*Escherichia coli* (2), *Klebsiella pneumoniae* (1), mixed culture with *Enterococcus* spp. and *E. coli* (1)]. Fifteen (15/26) urine samples were sterile, three were polymicrobial. In eight cases, urine culture revealed *E. coli* growth (one *E. coli* and *Enterococcus* spp.). Three out of 16 (3/16) surgical incision samples revealed growth of *E. coli*. No bacterial growth was detected in blood cultures. Susceptibility results of Gram-negatives indicate that the resistance rates of beta-lactam antibiotics are high (14/20, 70%). No secondary surgical intervention occurred during the study period due to infection.

Conclusions: Majority of postpartum cervical discharge, fever, and increased CRP levels do not represent morbid infections and/or sepsis. With early detection, and implementation of antibiotherapy (combination of an aminoglycoside and clindamycin), they can be easily controlled and secondary surgical interventions can be prevented.

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Introduction

Morbidly adherent placenta (MAP) is a term defining the abnormal invasion of the trophoblast through the limiting Nitabuch's membrane. MAP is classified as accreta, increta, and percreta according to the depth of myometrial invasion. With the increased cesarean section (CS), incidence of MAP has increased from 1/10,000 to current incidence of 1/533 pregnancy [1]. Moreover, maternal mortality is reported to be as high as 7% [2]. Conventionally, peripartum hysterectomy has been the standard treatment in patients with MAP. However, the operation is associated with significant risk of maternal mortality, genitourinary injury (6–29%), massive transfusion (13%), and reoperation (33%) [3–7]. Therefore, conservative, uterine sparing approaches for the management of MAP have been described to reduce both morbidity of peripartum hysterectomy and to spare future fertility.

Leaving placenta *in situ* (LPIS) is relatively a novel approach for preserving uterus and avoiding life-threatening hemorrhage. Recent American survey showed that 32% clinicians had attempted to LPIS as a way of conservative management [8]. The basic principle in this approach is to avoid from placenta while performing uterine incision and manipulating uterus after the delivery of the baby. After the delivery, placenta is expected to be disappearing by means of both resorption and piecemeal expulsion. However, this process has been reported to be open to the life-threating infection and even might lead to maternal death [9,10].

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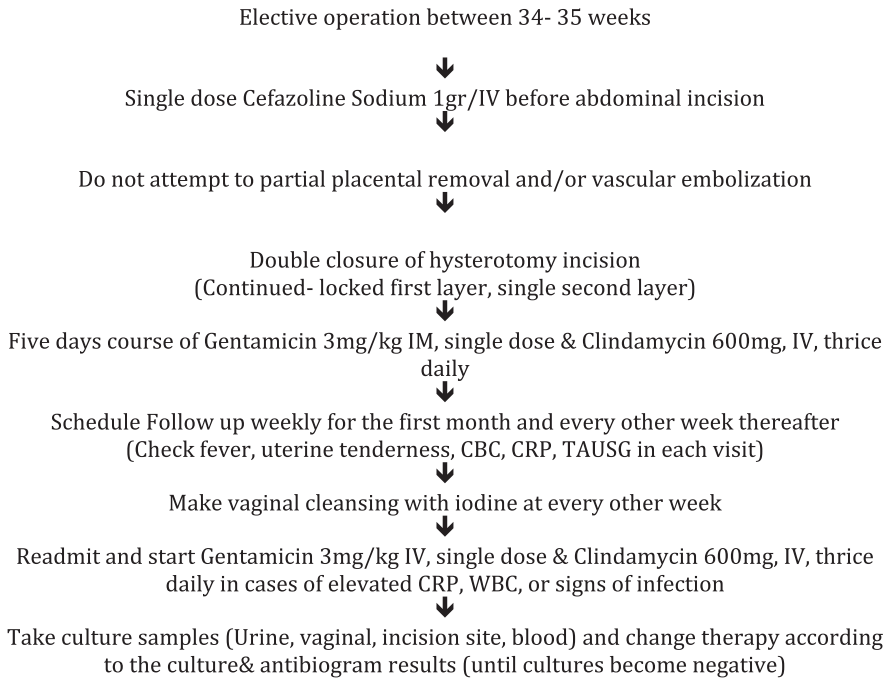

CBC Complete blood count, CRP C- reactive protein, TAUSG transabdominal ultrasonography, IV intravenous, WBC white blood cells

Figure 1. Suggested conservative approach for the management of morbidly adherent placenta.

With this background, we assessed the potential signs and markers of clinical infections, microbiological properties, and antibiotic susceptibility of clinical specimen taken from patients treated with leaving placenta *in situ*. Additionally, based on the aforementioned data, we tried to present clues for the follow-up and treatment of these patients.

Materials and methods

In this retrospective cohort study, the data of cases with morbidly adherent placenta treated with leaving placenta *in situ* at Erciyes University between 2 May 2010, and 15 March 2017 was collected. Fifteen of these cases were reported in our previous study, which compares the clinical outcome of MAP cases treated with LPIS and conservative/radical surgery [11]. The Institutional ethical board of Erciyes University approved the study.

Patients with placenta increate or percreta who opted for fertility sparing management were included in the study. The patients were assessed with both transvaginal and transabdominal ultrasonography probes (Voluson 730 Pro; GE Healthcare, Zipf, Austria). The diagnosis of PAS disorder was made when the following ultrasonographic criteria were met (i) presence of placental lacunae containing vascular flow by Doppler US, (ii) retroplacental placental thickness less than 1 mm, (iii) obliteration of the normal hypoechoic retroplacental zone, and (iv) irregularity of the bladder–myometrium interface [3]. Patients, who were below 24 gestational weeks, were not diagnosed antenatally, and presented with bleeding, and whose data were incomplete were not included in the study.

Cesarean section was performed via midline periumbilical abdominal, and classical uterine incision. The uterine incision was performed near to the fundus so as not to pass through placenta. Umbilical cord was tied with absorbable sutures and cut at the placental insertion site after delivery. Hysterectomy incision was double-layered closed with no 1 polyglactin suture (Vicryl, Ethicon, Somerville, NJ, USA), and abdominal suction drain was placed. Clindamycin (Clindan 600 mg, IV, TID, Bilim Ilaç, Istanbul, Turkey), and gentamycin (Genta 3 mg/kg, IV, Ibrahim Etem Ulagay, Istanbul, Turkey) combination were administered for 5 days in the hospital. Patients were seen weekly in outpatient clinic and their C-reactive protein (CRP), complete blood count tests were checked. Patients were also evaluated for uterine tenderness, and foul vaginal discharge. Vaginal cleaning with povidone iodine was applied for every other week. Patients were readmitted to the hospital when the following were observed: (I) high fever ($>38\,^{\circ}C$), (II) increased white blood cells, and CRP levels, (III) uterine tenderness, and foul smelling discharge, (IV) vaginal bleeding (Figure 1).

In patients who had copious and/or foul smelling discharge, lower abdominal pain, uterine tenderness, dysuria, sign of inflammation on incision sites, sample for culture were taken according to the possible source(s) of infection [11]. Sample from cervix were taken by gently pressing the uterine fundus from the abdomen. In cases of fever without localizing sign, sample for cultures were taken from all possible sites [urine, blood, cervical, and surgical incision site (SIS)]. The site of infections, the time infection occurred, clinical and laboratory features, culture and antibiotic resistance tests was noted.

The cervical swab specimens were inoculated onto a sheep blood agar (BA) plate, and onto a chocolate agar plate (Oxoid Ltd, Altrincham, United Kingdom). Chocolate agar was incubated in candle Jar to provide an increased CO_2 tension 5–10%.

Urine samples and specimens obtained from SIS were inoculated onto BA (Oxoid Ltd, Altrincham, United Kingdom) and eosin methylene blue Agar (Oxoid Ltd, Altrincham, United Kingdom) simultaneously. Samples are incubated overnight aerobically at 37 °C.

The BactAlert 3D BioMérieux (Lyon, France) automated blood culture system, and Kirby–Bauer disk diffusion methods were used for identification of the strains at species level and for the antibiotic susceptibility tests.

The statistical analyses were basically descriptive. The descriptive data were expressed as percentage. The normally distributed variables were presented as mean ± standard deviation, and asymmetrically distributed variables were presented as median ± min–max. The statistical analyses were performed with R program.

Findings

Twenty MAB cases were treated by LPIS during the study period. Fourteen cases (70%) were percreta and six (30%) cases were increta. One case required emergency hysterectomy due to severe bleeding a day after the procedure and that case was not included in the final analysis. The mean ± SD maternal age was 30.5 ± 4.7 years, the mean ± SD gestational age at delivery was 250 ± 12 days, the mean ± SD birth weight was 2402 ± 651 g, the mean ± SD duration for total placental resorption was 145 ± 47 days. The mean ± SD time for beta human chorionic gonadotropin clearance was 72 ± 17.2 days.

Three patients were readmitted to the hospital because of fever (3/19) and all responded well to the initial empiric antibiotic treatment. E. coli and, mixed infection with *E. coli* and *Enterococcus* spp. were isolated from the cervical culture of the first and second cases, respectively. Microbiological samples from the third patient yielded no causative agents. While first and the third cases had elevated CRP (70.8 and 97 mg/L, respectively), CRP was normal in the second case (3.1 mg/L). All urine and blood cultures were sterile and white blood cell count were normal in all three febrile cases ($8.6 \times 10^3/mm^3$, $10.2 \times 10^3/mm^3$, $11 \times 10^3/mm^3$, respectively). All febrile cases occurred between 37 and 57 days after the delivery.

Table 1. The culture results from the biological samples taken from cases with morbidly adherent placenta treated with leaving placenta *in situ*.

Culture site	Positive culture *n*(%)	Agents (*n*)
Cervical	4/12(33)	*E. coli* (2)
		K. pneumoniae (1)
		Enterococcus spp. and *E. coli* (1)
Urine	11/26(42)	*E. coli* (7)
		Enterococcus spp. and *E. coli* (1)
		Polymicrobial (3)
Surgical site	3/16(19)	*E. coli* (3)
Blood	0/11	–

A total of 65 culture samples were taken from the patients during their follow-up periods. Of these, 16 were surgical incision sites, 12 were cervical, 11 were blood, and 26 were urine. Clinical specimens yielding a positive culture were obtained between 39–113 days after delivery.

In four cases (4/12, 33%) cervical samples showed positive growth [two *E. coli* (1000 cfu *each*), one *K. pneumoniae* (5000 cfu), one *Enterococcus* spp. (1000 cfu), and *E. coli* (10,000 cfu)]. Two of these cases had high fever and the two were afebrile. They all had foul smelling discharge. WBC was normal in all four cases and CRP was elevated in two of the four cases with positive vaginal culture. Blood, incision site, and urine culture were sterile in these cases. Fifteen (15/26, 57.7%) of urine samples were sterile, three were polymicrobial. In seven cases, urine culture revealed *E. coli* (50,000–100,000 cfu) growth and one culture showed *E. coli* (10,000 cfu) and *Enterococcus* spp. (1000 cfu). Out of 16 surgical incision site samples, three (3/16, 18.8%) revealed growth of *E. coli* (5000–10,000 cfu). No bacterial growth was detected in blood cultures (Table 1).

In patients with positive culture for cervix, one had elevated CRP (31 mg/L) and cervical discharge, one had elevated CRP (70.8 mg/L) and high fever, two had foul smelling cervical discharge, spotting, and normal CRP levels. The cervical culture revealed bacterial growth between 51 and 113 days postpartum.

Five of 9 (5/9) Gram-negative bacilli were extended spectrum beta lactamase (ESBL) producing. Rates of

susceptibility of Gram-negatives obtained from SSIs ($n = 4$) were 1/4 for amoxicillin/clavulanate, 4/4 for ciprofloxacin, 4/4 for amikacin/gentamicin, and 1/4 for third generation cephalosporin. Rates of susceptibility for Gram-negatives obtained from urine cultures of patients (*n*: 6) were 2/6 for ciprofloxacin, 2/6 for amoxicillin/clavulanate, 4/6 for amikacin/gentamicin, 1/6 for third generation cephalosporins. Cervical cultures ($n = 4$) of patients were susceptible 2/4 for ciprofloxacin, 2/4 for amoxicillin/clavulanate, 4/4 for amikacin/gentamicin, and 1/4 for third generation cephalosporins. All symptomatic patients responded to antibiotic therapy and no secondary surgical intervention was performed because of infectious etiology. Also, no case of sepsis, disseminated intravascular coagulation, and intensive care admission occurred in this series.

Discussion

Our results showed that despite the high local infection rate, the incidence of bacteremia and sepsis is quite low in appropriately managed patients whose placentas are retained due to MAP. The second most important result of our study is that *ex utero* discharge is generally a sign of decaying placental mass rather than pyometra. Previous studies showed that local and systemic infections are the major cause morbidity and mortality in conservatively managed MAP cases [9,10]. Despite accumulated clinical data regarding conservative management of MAP, our clinical knowledge about the microbiological and clinical features of these infections is limited to couple of case reports. According to the available limited literature, the common etiologic agent after cesarean section in all clinical cases was *E. coli* [12–14]. In some cases, pelvic and/or systemic infection has been caused by mix infection including *E. coli* combined with *Enterobacterium cloacea* [12], *Prevotella corporis, and Prevotella* [13]. Zhong et al. studied the microbiological characteristics of vaginal culture after the vaginal delivery complicated with MAP, and placenta is left *in situ*. Their results demonstrated that *E. coli* is the most common agent causing endometritis followed by *Enterococcus faecalis, Candida, Staphylococcus aureus,* and *epidermidis*, bird enterococci plus Gram-positive cocci [14]. Summary of the literature regarding the microbiological etiology in PLIS cases is presented in Table 2.

According to the our institutional protocol, placenta is left *in situ* totally in conservatively treated MAP cases and no additional sutures are placed on the edge of the placenta. Moreover, we do not intend to remove placenta neither postoperatively nor in response to local infection. Previous reports describing serious infectious morbidity had some common features; partial removal of the placenta at the cesarean section [13], attempt to remove placenta [12,13], vaginal delivery [13,14], methotrexate administration [9], and uterine artery embolization [15,17]. However, in some cases no predisposing factor could be identified [16]. In one of the largest retrospective series including 167 cases, Senthiles et al. reported that 78% of women retained their uteruses [9]. However, they reported 22% delayed hysterectomy rate, and 10 women experienced serious morbidity such as sepsis, vesicouterine fistula, and uterine necrosis. In their series, the rate of methotrexate use was 12%, and 50.9% of cases had undergone partial removal of placenta intraoperatively. Additionally, 37.1% of cases had vascular embolization procedures [9]. Similarly, Clausen et al. studied 36 cases of "placenta left-*in situ*" and reported 58% delayed hysterectomy and 25% infection rate [10]. However, the study group they presented was quite heterogeneous in terms of adjuvant procedures, prenatal diagnosis, and the amount of placenta being left *in situ* [10]. Unfortunately, there is no data with regard to antibiotic prophylaxis, nature of the infectious complications, postoperative follow-up and treatment protocols in the previous series we cited above. Additionally, the role of interventional radiologic technics in the management of these cases should be carefully tailored as their use was shown to be associated with serious infections and uterine necrosis, and disseminated intravascular coagulation [17,18].

Given the nature of risk factors, leaving placenta *in situ* in an uncontaminated condition is of capital importance in preventing serious infection. Accordingly, our postpartum aggressive, wide spectrum antibiotic therapy seems to contribute to the

Table 2. Summary of the literature regarding the microbiological etiology in morbidly adherent placenta treated with leaving placenta *in situ*.

References	Microbial agent (site of culture sample)	*n*
Present series	*Escherichia coli* (cervical)	2
	Klebsiella pneumoniae (cervical)	1
	Enterococcus spp and *E. coli* (cervical)	1
Chiang et al. [12]	*Enterobacterium cloacea and E. Coli* (vaginal)	1
Hunt et al. [13]	*P. corporis* (*blood*)	1
	Prevotella (blood)	1
	E. coli (wound)	1
	Nonhemolytic streptococcus (wound)	1
Zhong et al. [14]	*E. coli* (Blood)	9
(Vaginal delivery)	*E. faecalis* (blood)	6
	Candida (blood)	3
	Staphylococcus aureus and epidermidis (blood)	1
	Bird enterococci plus Gram-positive cocci (blood)	2
Khan et al. [15]	*E. coli* (vaginal)	1
Morel et al. [16]	*E. coli* (vagina and blood)	1

eradication of local bacterial flora and potential intraoperative contamination. Our results demonstrated that infection of uterine cavity/placenta occurs between 51 and 113 days postpartum. According to our observations, this time frame corresponds to cessation of blood flow to the placenta. It theoretically seems plausible that ischemic placenta become susceptible to the infection due to diminished immune protection and increased discharge of necrotic material, which provides fertile soil for the colonized bacteria. Still another observation of this study was that two of the four cases with positive culture had normal CRP levels. It is important to note that no perfect biochemical marker exist to detect infection in these cases, and postpartum evaluation of these cases should focus both on physical signs and microbiological/biochemical findings of infection.

Urinary tract infections were the most common form of infection in this study. In contrast to placental/endometrial infections, UTI may be seen in the early postpartum period. Four of eight UTI were seen within 19 days of cesarean section, and rest of the cases distributed from 4 to 175 days. Therefore, UTI should be kept in mind as cause of puerperal infections in these cases and routine urine culture should be performed weekly in the first month after delivery and monthly thereafter.

Susceptibility results of Gram-negatives obtained from clinical specimens of patients indicate that the resistance rates of beta-lactam antibiotics are high. Also, considering the fluoroquinolones are not safe in breastfeeding, combination of an aminoglycoside with an anti-anaerobic agent appears to be a viable option in case of any episode of infection. However, empirical therapy should also be based on local epidemiological data of antimicrobial susceptibility. In an institution with a high prevalence of ESBL producers, as we reported in this current study, piperacillin-tazobactam or a carbapenem can be used empirically.

The major limitations of this study were its retrospective design and small cohort. In addition, lack of data regarding vaginal culture of those patients without signs and symptoms of infection prevent us from understanding the role of bacteria (colonization versus infection) in the pathogenesis of infection in these cases.

In conclusion, leaving placenta *in situ* is an effective and safe option to cesarean hysterectomy in MAP. Majority of signs and symptoms of infections in these cases are amenable to medical treatment without secondary surgical interventions. With strict adherence to surgical principles and judicious use of antibiotics, it is possible to increase the number of cases treated conservatively and reduce the rate of serious complications.

Disclosure statement

No potential conflict of interest was reported by the authors.

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