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Evaluation of the efficacy of vaginal progesterone in preventing preterm birth after abdominal trachelectomy: a prospective study with a historical cohort

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Abstract

Objective To determine whether vaginal progesterone (VP) reduces the rate of preterm birth in pregnant women after abdominal trachelectomy (AT) for early-stage cervical cancer Design Prospective cohort study with a historical cohort Setting University hospital Population Twelve pregnancies in ten women were included in the VP group between October 2016 and September 2020. By contrast, 19 pregnancies in 17 women were included in the historical control group between January 2007 and September 2016. Methods For the interventional study participants, the administration of vaginal progesterone was started between 16+0 and 19+6 weeks of gestation and discontinued at 34 weeks of gestation or at the time of delivery, rupture of membranes, or massive uterine bleeding, whichever occurred first. We investigated obstetric and neonatal outcomes among the study participants and compared them with outcomes of the historical control group participants. Main Outcome Measures The gestational age at delivery and incidence of preterm birth before 37 weeks and 34 weeks of gestation Results The incidence of preterm birth at <37 weeks was 10/12 (83%) in the VP group and 11/19 (58%) in the control group, and the incidence of preterm birth at <34 weeks was 6/12 (50%) in the VP group and 9/19 (47%) in the control group. The incidence of preterm birth in the two groups was similar, and the difference between the two groups was not statistically significant. Conclusions The administration of vaginal progesterone did not reduce the rate of preterm birth among pregnant women after AT.

Title: Evaluation of the efficacy of vaginal progesterone in preventing preterm birth after abdominal trachelectomy: a prospective study with a historical cohort

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Running title

Progesterone to prevent post-AT preterm birth

[Abstract]

Objective

To determine whether vaginal progesterone (VP) reduces the rate of preterm birth in pregnant women after abdominal trachelectomy (AT) for early-stage cervical cancer

Design

Prospective cohort study with a historical cohort

Setting

University hospital

Population

Twelve pregnancies in ten women were included in the VP group between October 2016 and September 2020. By contrast, 19 pregnancies in 17 women were included in the historical control group between January 2007 and September 2016.

Methods

For the interventional study participants, the administration of vaginal progesterone was started between 16^{+0} and 19^{+6} weeks of gestation and discontinued at 34 weeks of gestation or at the time of delivery, rupture of membranes, or massive uterine bleeding, whichever occurred first. We investigated obstetric and neonatal outcomes among the study participants and compared them with outcomes of the historical control group participants.

Main Outcome Measures

The gestational age at delivery and incidence of preterm birth before 37 weeks and 34 weeks of gestation

Results

The incidence of preterm birth at <37 weeks was 10/12 (83%) in the VP group and 11/19 (58%) in the control group, and the incidence of preterm birth at <34 weeks was 6/12 (50%) in the VP group and 9/19 (47%) in the control group. The incidence of preterm birth in the two groups was similar, and the difference between the two groups was not statistically significant.

Conclusions

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The administration of vaginal progesterone did not reduce the rate of preterm birth among pregnant women after AT.

Funding

None

Keywords

abdominal trachelectomy, vaginal progesterone, preterm birth, preterm premature rupture of membranes

Tweetable abstract

Vaginal progesterone did not reduce the preterm birth rate among pregnant women after abdominal trachelectomy.

[Introduction]

Abdominal trachelectomy (AT) has been used as a fertility-sparing surgery for early-stage cervical cancer in women of reproductive age since the first report (Smith JR, 1997) on the same was published,[1] and is defined as surgical removal of the uterine cervix with preservation of the uterine body. The incidence of cervical cancer in reproductive-aged women is increasing,[2-4] and the number of women desiring pregnancy after AT is also increasing accordingly. Many reports on obstetric outcomes in pregnant women after AT in the past have described the high risk of miscarriage, preterm birth, and preterm premature rupture of membranes (pPROM).[5-9] The reported incidence of preterm birth and miscarriage ranges from 53% to 89%,[6-10] and the high rate of complications in pregnant women after AT can be attributed to the loss of the supporting tissue of the cervical canal that maintains pregnancy and ascending infection due to the loss of the cervical mucus plug. Although the high risk of miscarriage has recently been well recognized, a preventive approach for pregnancies after AT has not been discussed.

The efficacy of progesterone administration in preventing preterm birth in high-risk pregnant women such as those with a history of preterm birth[11,12] or women with a shortened cervix[13,14] has recently been established, and the use of this drug for managing such high-risk pregnancies has become common in Western countries.[15,16] The mechanism of action of progesterone responsible for preventing preterm birth has not been fully determined, but the preventive effect is speculated to be caused by its anti-inflammatory effect, decreased cervical stromal degradation, and a decreased frequency of contractions of the myometrium.[17] The efficacy of progesterone in preventing preterm birth in high-risk pregnancies is unquestioned; however, to the best of our knowledge, the use of progesterone for reducing the risk of preterm birth in pregnant women after AT has not been reported to date.

Against this background, we designed an interventional study to determine whether vaginal progesterone (VP) reduces the rate of preterm birth in pregnant women after AT.

[Methods]

Study population and design

This was a prospective interventional study that commenced in October 2016. The Kyushu University Hospital Ethical Review Board approved the study, and all work was conducted in accordance with the Declaration of Helsinki (1964). The enrollment criterion was women with singleton pregnancies after the second trimester who had previously undergone AT for early-stage uterine cervical cancer at our hospital. The exclusion criteria were abortion during early pregnancy, contraindications for progesterone use, multiple pregnancies, women who had undergone AT in other hospitals, and fetuses with severe anomalies or abnormal chromosomes. Eligible women were invited to participate in this study and sign a consent form. After obtaining informed consent, we started vaginal progesterone administration.

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The primary outcomes of our study were gestational age at delivery and the incidence of preterm birth before 37 weeks and 34 weeks of gestation. The secondary outcomes were the incidence of pPROM and other obstetric complications, maternal adverse events (transfusion for massive vaginal bleeding, hysterectomy after cesarean section, septic shock, and maternal death), and neonatal morbidity and perinatal mortality (fetal death and neonatal death). We investigated these outcomes among the study participants and compared them with those of the historical control group participants. The historical control group included women with singleton pregnancies after AT who were managed without VP at our institution between January 2007 and September 2016. Data of the historical control group participants were collected retrospectively by reviewing both maternal and neonatal medical records of each participant. In 2017, we reported the perinatal outcomes of singleton pregnancies after AT[18] managed between March 2005 and October 2015, and the historical control group in this study partly overlapped with that reported in the previous study.

Administration of vaginal progesterone

For the study participants, administration of vaginal progesterone was started between 16^{+0} and 19^{+6} weeks of gestation. We used 200 mg vaginal progesterone capsules (UTROGESTAN® vaginal capsules 200 mg, Fuji Pharma Co., Ltd., Japan). The women self-administered the tablets vaginally once daily at night. Progesterone administration was discontinued at 34 weeks of gestation or at the time of delivery, rupture of membranes, or massive uterine bleeding, whichever occurred first. At approximately 26 weeks of gestation, study participants were examined for side effects of progesterone through the following blood tests: (1) liver function: aspartate aminotransferase [AST] and alanine aminotransferase [ALT] and (2) coagulation function: D-dimer, and further tests were conducted if the test results were abnormal.

Institutional management policy for pregnancies after abdominal trachelectomy

We checked for the presence of vaginal varices at the uterovaginal anastomotic site. Pregnant women after AT were routinely hospitalized after 30 weeks for anticipated acute bleeding from vaginal varices. The mode of delivery was determined as cesarean section and planned at 37 weeks of gestation if the pregnancy progressed uneventfully. Cesarean section was routinely performed because a permanent cervical cerclage was placed during abdominal trachelectomy.

If threatened preterm delivery due to frequent uterine contractions was suspected on cardiotocography, tocolytic agents including oral calcium channel blockers (Ca-blockers), intravenous magnesium sulfate, or ritodrine were administered as required. When pPROM occurred prior to 34 weeks of gestation, antenatal corticosteroids, and prophylactic antibiotics (ampicillin and clindamycin) were administered. When the pregnancies reached 34 weeks of gestation without spontaneous labor onset or development of clinical chorioamnionitis (cCAM) even after pPROM, a cesarean section was performed at 34 weeks of gestation. If labor commenced or cCAM was diagnosed during expectant management of pPROM, a cesarean section was immediately performed. cCAM was diagnosed by an axillary temperature >38.0 °C and at least one of the following signs: heart rate >100 bpm, serum white blood cell count >15,000/μL, and C-reactive protein level of >2.0 mg/dL. When pPROM occurred after 34 weeks of gestation, a prompt cesarean delivery was performed.

Statistical analysis

Non-normally distributed data are reported as median and range. We compared the two groups using Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY).

[Results]

During the study period, 12 pregnancies in ten women were included in the VP group. In contrast, 19 pregnancies in 17 women were included in the historical control group. Results from the comparison of the oncological background characteristics of the ten women in the VP group and 17 women in the historical control group, and the baseline maternal characteristics of the 12 pregnancies in the VP group and 19

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pregnancies in the historical control group are shown in Table 1. The cancer stage and operative procedures were similar in the two groups. Age at delivery and the rate of assisted reproductive technology use were similar between the two groups; one egg donation-embryo transfer was noted in the VP group. The median duration between surgery and delivery was somewhat longer in the VP group than in the control group, but the difference was not statistically significant.

Table 2 shows the pregnancy and perinatal outcomes. The incidence of preterm birth at <37 weeks was 10/12 (83%) in the VP group and 11/19 (58%) in the control group, and the incidence of preterm birth at <34 weeks was 6/12 (50%) in the VP group and 9/19 (47%) in the control group. The difference in the incidence of preterm birth between the two groups was similar and not statistically significant. The most common cause of preterm emergency cesarean section was pPROM in both groups. Figure 1 shows the distribution of gestational age at delivery in both groups. The median gestational age at delivery was 33^{+6} weeks (range: 26^{+0} to 37^{+4} weeks) in the VP group and 34^{+6}weeks (range: 23^{+5} to 37^{+5} weeks) in the control group. No miscarriages (delivery <22 weeks) occurred in either group. The incidence of pPROM was 6/12 (50%) in the VP group and 8/19 (42%) in the control group. The median gestational age at pPROM tended to be earlier in the VP group than in the control group, although the difference was not statistically significant. In the VP group, intrauterine fetal death occurred at 32 weeks of gestation in one case. The fetal anatomic survey was unremarkable, and the cause of fetal death was undetermined. Other pregnancy and perinatal outcomes were similar between the two groups.

Table 3 shows the maternal adverse events. Of the total number of pregnant women, abnormal massive vaginal bleeding from vaginal or cervical varices during pregnancy occurred in eight women, and three women from the VP group and four from the control group required blood transfusion. In the control group, total abdominal hysterectomy (TAH) after cesarean section was performed in two women. The indications for TAH were placenta accreta in one and septic shock due to the development of an intra-abdominal abscess following cesarean section in another. In the VP group, no side effects of progesterone were noted.

Table S1 shows the neonatal outcomes of the 30 liveborn infants. In the control group, an infant death occurred in one case. The birth weight, number of admissions to the Neonatal Intensive Care Unit, and other neonatal outcomes were similar in the two groups. Of the study participants, 17 infants have already reached 1.5 years of corrected age. Regarding neurodevelopmental outcomes, in the control group, cerebral palsy was noted in one of the infants. None of the infants had mental retardation or epilepsy.

[Discussion]

Main findings

Our study suggested that vaginal progesterone was ineffective in preventing preterm birth in pregnant women after AT. The incidence of preterm birth at <34 weeks and at <37 weeks and gestational age at delivery were similar between the VP and control groups.

Strengths and Limitations

This is the first interventional study to investigate the prevention of preterm birth in pregnant women after AT and describe the obstetric and antepartum complications in detail. One limitation of our study was the absence of randomization. However, the study groups were separated by a time period, and clinicians could not use their discretion to determine whether vaginal progesterone should be administered. Therefore, we believe that the backgrounds in both groups were similar and that our study has a certain level of precision as a comparison analysis. Another limitation was the small sample size. Initially, we had planned to accumulate data from a larger sample size for a longer study period; however, based on the apparently ineffective results presented herein, the only alternative was to stop this interventional study early, considering that any study in a clinical setting should be performed on behalf of patients.

Interpretation

Our study showed a high incidence of preterm birth (58%) in the control group (without VP), and the median

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gestational age at delivery was 34 weeks. These findings were consistent with those of previous studies analyzing obstetrical outcomes of pregnant women after AT.[3-7] Furthermore, the incidence of pPROM in the control group was 42%, which was the main cause of preterm birth. Preterm birth in pregnant women after AT is believed to be due to the loss of the supporting tissue of the cervical canal that maintains pregnancy and ascending infection resulting from the loss of the cervical mucus plug, which may contribute to pPROM.[19]Complications associated with prematurity may greatly impair the development and quality of life of a preterm infant, even after long-term survival; therefore, it is important that obstetric clinicians make consecutive efforts to prevent preterm birth. Based on these findings, we conducted this study to administer progesterone supplements to pregnant women who had undergone AT in anticipation of its preventive effect on preterm birth.

Progesterone plays an important role in the maintenance of pregnancy. Circulating levels of progesterone rise during pregnancy, and destruction of the corpus luteum, the main source of progesterone during early pregnancy, leads to spontaneous abortion/miscarriage. There is convincing evidence regarding its role in reducing the incidence of preterm birth. Progesterone includes natural progesterone administered vaginally (vaginal progesterone) and 17-alpha-hydroxy-progesterone-caproate (17-OHP) administered intramuscularly. Vaginal progesterone and 17-OHP are both considered effective in preventing preterm birth, and both have been administered to eligible pregnant women at high risk of preterm birth.[11,20]

It remains controversial whether 17-OHP or vaginal progesterone is more effective in preventing preterm birth in women with a history of preterm birth. Some studies[11,12] have found 17-OHP to be superior in this regard, and the American College of Obstetricians and Gynecologists (ACOG)[21] and the Society for Maternal Fetal Medicine (SMFM)[17] recommend the use of the former. On the other hand, some studies[22,23] have suggested vaginal progesterone to be superior, and the Society of Obstetricians and Gynecologists of Canada (SOGC) guidelines recommend the use of vaginal progesterone.[24] In Japan, data regarding this drug is still lacking, and it has not been recommended by the guidelines. In this study, we selected vaginal progesterone as it could be inserted by the women themselves, and we expected to achieve favorable medication compliance. However, the administration of vaginal progesterone did not reduce the preterm birth rate in our study, and the incidence of pPROM and histologic chorioamnionitis (hCAM; stage >II) did not decrease. The mechanisms of action of progesterone responsible for preventing preterm birth are believed to include its anti-inflammatory effects, ability to reduce cervical stromal degradation, and ability to inhibit myometrial contractions,[16,17] but these mechanisms remain to be fully determined. The negative data presented herein suggest that the presence of the uterine cervix is essential for vaginal progesterone to exert a preventive effect on preterm birth.

On the other hand, seven women required blood transfusion due to massive bleeding from cervical varices and two underwent TAH after cesarean section due to antepartum complications. In particular, two of the seven women who required blood transfusion went into preterm labor because of the massive bleeding (at 28 weeks and 34 weeks). We have previously discussed the significance of vaginal and cervical varices in the management of pregnancies after trachelectomy,[18] and we speculated that venous pressure could increase during pregnancy, inducing varix formation at the uterovaginal anastomotic site. Although the management of vaginal and cervical varices in pregnant women after AT needs to be discussed further,[7] we believe that variceal bleeding may also induce preterm labor, and it should be recognized as an important complication in the management of pregnancy after AT.

Conclusion

The administration of vaginal progesterone did not reduce the rate of preterm birth among pregnant women after AT. This negative result suggests that the existence of the uterine cervix is essential for the preventive effect of progesterone on preterm birth.

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[Disclosure of Interests]

None declared; the completed disclosure of interests from is available online as supporting information.

[Contribution to Authorship]

Y.S., N.H., and K.K. conceived the study. Y.S. and N.H. carried out data research and wrote the manuscript. A.S., S.K., Y.F., K.O., H.Y., and K.K. contributed to the discussion and reviewed the manuscript.

[Details of Ethics Approval]

This study was approved initially by the Kyushu University Institutional Review Board for Clinical Trials, Fukuoka, Japan, Aug. 5, 2016 (Trial ID: UMIN000023161). However, the Clinical Trials Act came into force in Japan, April 2018. By the new act, all clinical trials which correspond to the legal requirements have been required to be registered to the new official database "jRCT". Therefore, this study was reviewed again and approved by the Kyushu University Certified Institutional Review Board for Clinical Trials which has been established by the new act, March 29, 2019 (Trial ID: jRCTs071180085).

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None

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Table captions

Table 1. Oncological background of 27 women who underwent abdominal trachelectomy and maternal characteristics of 31 pregnant women

	Total	VP group	Control group	P-value
Oncological backgraound	N=27	N=10	N=17	
Age at operation (years old)	32 (26-39)	32 (26-38)	31 (26-39)	N.S.
Cancer stage				
CIN3	1 (4)	1 (10)	0 (0)	N.S.
IA2	3 (11)	1 (10)	2 (12)	N.S.

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	Total	VP group	Control group	P-value
IB1	22 (81)	7 (70)	15 (88)	N.S.
IB2	1 (4)	1 (10)	0 (0)	N.S.
Histology				
Adenocarcinoma	11 (41)	4 (40)	7 (41)	N.S.
Squamous cell carcinoma	14 (52)	3 (30)	10 (59)	N.S.
Adenosquamous carcinoma	1 (4)	1 (10)	0 (0)	N.S.
CIN3	1 (4)	2 (20)	0 (0)	N.S.
Operative procedure				
AST	2 (7)	1 (10)	1 (6)	N.S.
AmRT	12 (44)	5 (50)	7 (41)	N.S.
ART	13 (48)	4 (40)	9 (53)	N.S.
Maternal characteristics	N=31	N=12	N=19	
Age at delivery (years old)	37 (28-45)	38 (30-45)	36 (28-41)	N.S.
Primipara	21 (68)	7 (58)	14 (74)	N.S.
ART	19 (61)	8 (67)	11 (58)	N.S.
IVF	12 (39)	5 (42)	7 (37)	
ICSI	6 (19)	2 (17)	4 (21)	
Egg donation-ET	1 (3)	1 (8)	0 (0)	
Duration between surgery and delivery (months)	46 (13- 133)	56 (13-133)	43 (16-105)	N.S.

Data are presented as the number (%) or median (range)

VP, vaginal progesterone; CIN, cervical intraepithelial neoplasia; AST, abdominal simple trachelectomy; AmRT, abdominal modified radical trachelectomy; ART, abdominal radical trachelectomy; ART, assisted reproductive technology; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; ET, embryo transfer; N.S., not significant

Table 2. Pregnancy and perinatal outcomes

Perinatal outcomes	Total N=31	VP group N=12	Control group N=19	P-value
GA at delivery (weeks)	34^{+0} (23^{+5}-37^{+5})	33^{+3} (26^{+0}-37^{+4})	34^{+6} (23^{+5}-37^{+5})	N.S.
Miscarriage (<22 weeks)	0 (0)	0 (0)	0 (0)	N.S.
Preterm birth	21 (68)	10 (83)	11 (58)	N.S.
<28 weeks	3 (10)	1 (8)	2 (11)	N.S.
[?]28 weeks, < 34 weeks	12 (39)	5 (42)	7 (37)	N.S.
[?]34 weeks, < 37 weeks	6 (19)	4 (33)	2 (11)	N.S.
pPROM	14 (45)	6 (50)	8 (42)	N.S.

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Perinatal outcomes	Total N=31	VP group N=12	Control group N=19	P-value
GA at pPROM (weeks)	30^{+3} (23^{+5}-35^{+1})	28^{+1} (24^{+5}-34^{+0})	32^{+1} (23^{+5}-35^{+1})	N.S.
Clinical CAM	2 (6)	0 (0)	2 (11)	N.S.
Histological CAM	5 (16)	3 (25)	2 (11)	N.S.
Stage I	0 (0)	0 (0)	0 (0)	N.S.
Stage II	1 (3)	1 (8)	0 (0)	N.S.
Stage III	5 (16)	2 (17)	3 (16)	N.S.
IUFD	1 (3)	1 (8)	0 (0)	N.S.
Reason for preterm birth				
cCAM	2 (6)	0 (0)	2 (11)	N.S.
PROM	7 (23)	2 (17)	5 (26)	N.S.
Labor onset	4 (13)	2 (17)	2 (11)	N.S.
Bleeding from varices	5 (16)	3 (25)	2 (11)	N.S.
Presumed fetal compromise	2 (6)	2 (17)	0 (0)	N.S.

Data are presented as the number (%) or median (range)

GA, gestational age; VP, vaginal progesterone; TPL, threatened premature labor; pPROM, preterm premature rupture of membranes; cCAM, clinical chorioamnionitis; IUFD, intrauterine fetal death; CS, cesarean section; N.S., not significant Table 3. Maternal adverse events

	Total (N=31)	VP group (N=12)	Control group (N=19)	P-value
Abnormal vaginal bleeding from varix	8 (26)	3 (25)	5 (26)	N.S.
Blood transfusion during pregnancy	7 (23)	3 (25)	4 (21)	N.S.
Sepsis	1 (3)	0 (0)	1 (5)	N.S.
TAH	2 (7)	0 (0)	2 (11)	N.S.
Death	0 (0)	0 (0)	0 (0)	N.S.

Data are presented as the number (%) or median (range)

VP, vaginal progesterone; TAH, total abdominal hysterectomy; N.S., not significant

Figure captions

Figure 1. Distribution of gestational age at delivery

VP: vaginal progesterone

Supporting information, Table 1. Neonatal outcomes of the 30 liveborn infants

Data are presented as the number (%) or median (range)

VP, vaginal progesterone; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; CLD,

chronic lung disease; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; DQ, developmental quotient; CP, cerebral palsy;

N.S., not significant

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`Figure_1.docx` available at https://authorea.com/users/468070/articles/561920-evaluation-of-the-efficacy-of-vaginal-progesterone-in-preventing-preterm-birth-after-abdominal-trachelectomy-a-prospective-study-with-a-historical-cohort

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