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Role of telocytes in the pathogenesis of ectopic pregnancy

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Abstract. – OBJECTIVE: The aim of this study is to investigate the effect of telocytes on tubal motility in ectopic pregnancies.

PATIENTS AND METHODS: This study included patients with ectopic pregnancy (EP) (n=10) and control patients (n=10) (partial salpingectomy for contraception). Immunohistochemical staining for c-Kit, vimentin, CD34 and S100A was performed to quantify telocytes in the mucosa, muscular layer and serosa of fallopian tubes of control and EP group. Spontaneous and KCl- (80 mM) induced contraction and cumulative progesterone dose-relaxation (10^{-11}-10^{-5} M) and cumulative oxytocin dose-contraction (10^{-10}-10^{-4} M) responses were recorded.

RESULTS: The groups were comparable in terms of age, gravida, parity, delivery type and gestational week (p>0.05). The homogenous distribution of telocytes in the mucosa and muscular layers of the control group, changed to heterogeneous localization the EP group. Immunohistochemical staining with vimentin, S100A, c-Kit and CD34, revealed increased telocyte counts in the muscular layer and serosa of the tubal tissues of EP. The frequency of the spontaneous contractions was higher in the control group (p<0.001); contrarily, the amplitude of the contractions was higher in ectopic pregnancies (p<0.001). Although the cumulative oxytocin dose-contraction curves were similar at all concentrations (p>0.05), the cumulative progesterone dose-relaxation curves exhibited higher relaxation response in the EP group at all concentrations (p<0.001).

CONCLUSIONS: Increased telocyte count in the fallopian tube may decrease tubal motility and may affect the transfer of the blastocyst to the uterus and possibly contribute to the pathogenesis of EP.

Key Words:
Telocytes, Fallopian Tubes, Ectopic pregnancy, Immunohistochemistry, Smooth muscle contraction.

Introduction

Ectopic pregnancy is the implantation of the blastocyst outside the endometrial lining of the uterine cavity. The most common site of ectopic pregnancy is the fallopian tube in 96 to 98% of cases[1,2]. The main problem in EP is transport of the blastocyst to the uterine cavity, which may be due to impaired tubal anatomy and/or function. Disruption of the tubal cilia and muscle alignment leads to tubal dysfunction. Infections, surgery, and congenital abnormalities may also play a role in the etiology of this anatomical and functional impairment[3]. Histologically, the fallopian tubes have three layers: mucosa, muscular layer, and serosa. The smooth muscle layer, which is located along the entire fallopian tube, is critical for tubal functions and structural integrity[4]. The interstitial cells of Cajal (ICC) are specialized smooth muscle cells located in the muscular layer and are involved in communication between the autonomic nervous system and smooth muscle cells. ICC have pacemaker activity and contribute to the contraction and/or relaxation of smooth muscle[4]. Telocytes are recently identified cells reported to be found in many organs in the human body serving various functions such as tissue repair and regeneration or pacemaker activity[5]. These cells are morphologically and functionally related to ICC. Current evidence suggests that

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telocytes are electrically active cells, capable of generating and transmitting slow waves and can transmit the electrical activity to smooth muscle cells and immune cells[6]. Regardless of the tissue in which they are found, telocytes have very long and thin cytoplasmic extensions called telopodes which serve to form a network with the other cells[7]. Since their first discovery in the uterine wall in the female reproductive system, in 2005, their existence has also been shown in the vagina, fallopian tubes and placenta[8,9]. Telocytes in the fallopian tubes express steroid hormone receptors which have been suggested to be involved in the regulation of tubal peristaltic movements modulated by progesterone and estrogen[7]. It has also been proposed that a change in the number and/or function of telocytes may cause pathologies such as endometriosis and ectopic pregnancies[7]. As a life-threatening gynecologic emergency and an important cause of all maternal deaths, it is very important to investigate pathophysiology of EP[10]. On this background, we aimed to investigate the number of tubal telocytes and their effects on tubal contraction-relaxation response and fallopian tube motility in patients with EP.

Patients and Methods

This prospective case-controlled study was conducted at Ankara Training and Research Hospital and Hacettepe University Medical Faculty. The study protocol was approved by the Hacettepe University Clinical Research Ethics Board (GO 17/445-49). Patients were invited to participate to the study if they had no previous history of tubal or ovarian surgery, ectopic pregnancy, sexually transmitted disease, pelvic inflammatory disease, endometriosis, adenomyosis or oral contraceptive use. Patients meeting the inclusion criteria and accepted to participate in the study were included after they gave their informed consent before they were submitted to the surgical procedure. Among the patients who accepted to participate in the study, those who were found to have silent pelvic infection, endometriosis, and congenital anomaly during the operations were excluded from the study. The study included patients who underwent salpingectomy due to ectopic pregnancy (study group, n=10) and who underwent partial salpingectomy for permanent contraception during cesarean section (control group, n=10). The salpingectomy materials were dissected into two pieces. One part of the surgical material was evaluated for routine pathological examination and the other piece from the ampullary region adjacent to the healthy border of the tissue where the ectopic pregnancy was located and corresponding areas in control patients was transferred to Hacettepe University Medical Faculty for histopathologic evaluation and electrophysiological experiments in appropriate medium, as described below.

Evaluation of Contraction-Relaxation Response

The salpingectomy material cleared of all surrounding tissues and four full thickness tissue strips (2x10 mm) were prepared in cold Krebs solution (118.4 mM NaCl, 4.7 mM KCl-, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 25.0 mM $NaHCO_3$, 2.5 mM $CaCl_2$, and 12.2 mM glucose; pH 7.35-7.40). The strips suspended in organ baths were allowed to equilibrate in Krebs solution gassed with 95% O_2 and 5% CO_2 mixture at 37°C under 0.5-1 g tension (washouts in every 15 minutes) at least for 45 minutes until spontaneous activity is observed. The strips were connected to the force displacement transducers (MAY FDT05, Commat, Ankara, Turkey). Mechanical activity was recorded real time by data acquisition/analysis system (BIOPAC MP36, Biopac Systems Inc., Goleta, CA, USA). Spontaneous contraction of the strips was recorded for 30 minutes, and contraction frequency and amplitude were evaluated. The strips were challenged by 80 mM KCl^- and maximum contraction response was recorded. Cumulative progesterone dose-relaxation (10^{-11}-10^{-5} M) and cumulative oxytocin dose-contraction (10^{-10}-10^{-4} M) responses were obtained by applying the higher dose to the bath every 10 minutes. One of the strips was reserved as time control (TC). After each protocol the organ baths were completely washed out three times and the strips were allowed to equilibrate again for at least 45 minutes. After all protocols were completed, the viability of the strips was checked by applying 80 mM KCl^- to all strips, and strips were weighed.

To determine location and examine morphologic and ultrastructural features of telocytes, tissues from control and EP group were fixed by 2.5% glutaraldehyde for 2 hours and 1% osmium tetroxide for 1 hour. Fixed samples were processed in Leica EM TP tissue processor (Leica Microsystems, Wetzlar, Germany) and embedded in plastic. Semi-thin sections were stained 1% methylene blue-azure II in 1% borax solution and evaluated

with light microscopy (Leica DM 6000, Leica Microsystems, Wetzlar, Germany). Ultrathin section was stained with uranyl acetate and lead citrate and visualized by JEOL-JEM 1400 electron microscope (Jeol Ltd, Tokyo, Japan).

Immunohistochemical staining was performed using vimentin, S100A, c-Kit and CD34 antibodies to show presence of telocyte and quantify in control and EP groups. Tissues were fixed with 10% neutral buffered formalin. Fixed tissues were processed (Leica TP 1020, Leica Microsystems Wetzlar, Germany) and embedded in paraffin (Leica Eg1150H, Leica Microsystems, Wetzlar, Germany). Transverse serial sections (5 µm) were deparafinized and rehydrated in decreasing concentration of ethanol. After washing with phosphate buffered saline (PBS), antigen retrieval was performed in citrate buffer and endogenous peroxidase was blocked by peroxide blocking buffer (Biolegend Ltd., San Diego, CA, USA). After permeabilization with 0.1% Triton X-100 for 10 minutes, unspecific binding was blocked with % 1 bovine serum albumin in PBS. Sections were incubated with primary antibodies [(c-Kit (1/200); vimentin (1/200); S100A (1/200); CD34 (1/1000)] overnight for 4oC and secondary antibody (Biolegend Ltd., San Diego, CA, USA) for 1 hour at RT. 3.3′-Diaminobenzidine was used as a chromogen and sections were stained with Mayer's hematoxylin for 1 min for counterstaining. Following dehydrating with graded alcohol series, sections were kept in xylene for 15 minutes and then covered with entellan and visualized using a brightfield light microscope (Leica DM6B, Leica Microsystems, Wetzlar, Germany) attached with a camera (BSC 7000T, Leica Microsystems, Wetzlar, Germany). Marked cells with antibodies in mucosa, muscular layer and serosa were counted in 5 randomly selected areas from each section of control and EP groups. For the semi-quantitative evaluation of immunostaining, H-score value was determined by using the formula H-SCORE=ΣPi(i+l), where i represents the intensity scores and Pi is the corresponding percentage of cells. The mean value of investigators' score was used for graphical and statistical calculations.

The contraction and relaxation data were analyzed by BSL Pro Version 3.6.7 software (Biopac Systems Inc., Goleta, CA, USA). The amplitude of contraction measurements was normalized to wet tissue weight as g/g wet tissue. Amplitudes of spontaneous or induced contraction and induced relaxation responses were expressed as percent of KCl^- induced maximum contraction, half maximal effective dose (EC50) for oxytocin and half maximal inhibitory dose (IC50) for progesterone were calculated, and frequency of phasic contractions was also evaluated.

Statistical Analysis

Statistical analysis for the Social Sciences version 22 (SPSS Inc, Chicago) data analysis program was used for statistical analysis. All values were expressed as median (min-max). Mann-Whitney U was used for comparison of nonparametric continuous variables and Fischer exact test was used for nominal variables. Statistical significance level was accepted as $p<0.05$.

Results

The study included 10 patients who had surgery for EP, and 10 patients who underwent permanent contraception during cesarean section and underwent bilateral partial salpingectomy.

Demographic and clinical findings of the patients are summarized in Table I. There was no significant difference between the two groups in terms of age, gravida, parity, type of previous delivery *(p*>0.05).

Table I. Demographic and clinical findings of the patients.

	Control (n = 10)	Ectopic pregnancy (n = 10)	*p*-value
Age (Years)	31.5 (25-41)	38 (30-44)	0.359*
Gravida	5 (2-8)	2 (1-8)	0.070*
Para	2.5 (1-4)	1 (0-4)	0.104*
BMI (kg/m^2)	27.2 (21.8-31.6)	22.5 (18.7-27.9)	0.048*
Previous Delivery (#)			
Vaginal	4	8	0.170**
Cesarean	6	2	

Values are given as median (min-max); BMI: Body mass index. *Mann Whitney U Test. **Fisher's Exact Test.

In the control group, telocytes were located around the vascular structures in the mucosa and muscular layer of the fallopian tube. These cells had small oval-shaped nuclei and thin elongated extensions. Extension of telocytes was seen as a thin prolongation that fits between the vascular structures in these layers. Telocytes showed homogeneous distribution in the muscular layer. In the EP group, however, telocytes were not homogeneously distributed in the mucosa and they were mostly located in areas away from the mucosa (Figure 1). Ultrastructural evaluation of the fallopian tube in EP group revealed the presence of telocyte with telopodes composed of podom and podomer around the capillaries and between the smooth muscle cells (Figure 2).

Vimentin, S100A, c-Kit and CD34 staining to quantify telocytes in control and EP group is presented in Figure 3.

The telocyte number in the mucosa was similar for all the antibodies in EP and control groups ($p>0.05$). In the muscular layer, the number of telocytes was higher in the EP group, however, this difference was significant only for S100A and CD34 ($p=0.006$ and $p=0.039$), but not for vimentin and c-Kit ($p>0.05$). The number of telocytes was also higher in the serosa of EP group, the difference was statistically significant for vimentin ($p=0.028$), S100A ($p=0.039$), and CD34 ($p=0.002$), except c-Kit ($p>0.05$) (Figure 4).

The H-scores exhibit similar staining intensity in all three of the examined layers in both groups ($p>0.05$). Spontaneous activity was different in EP and control groups, so that frequency was higher in the control group ($p<0.001$). However, the contraction amplitude was bigger in the EP group ($p<0.001$). The KCl^- induced

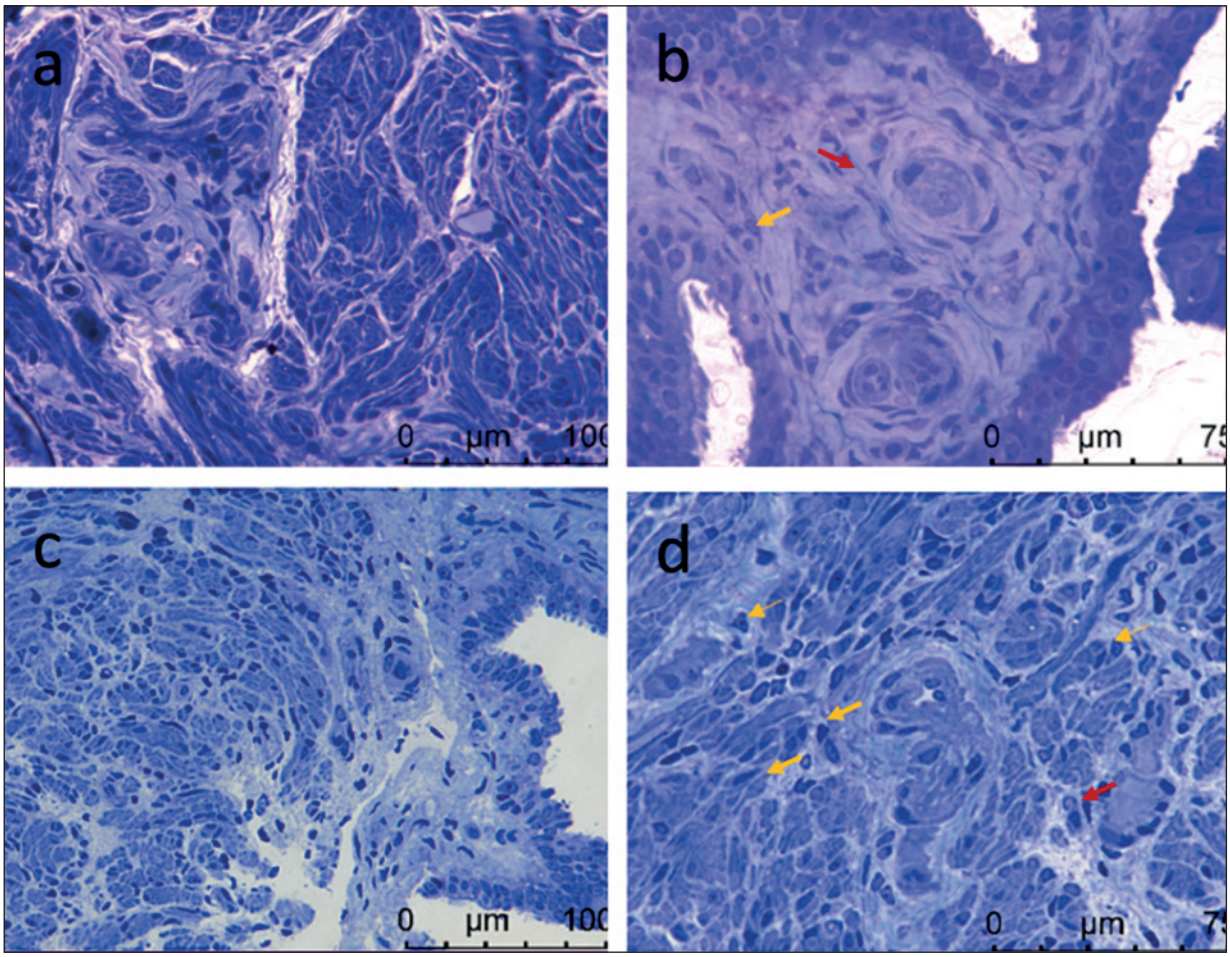

Figure 1. Light micrographs of fallopian tube from control and EP groups. **a,** (40×) and **b,** (63×) control group, **c,** (40×) and **d,** (63×) EP group. Yellow arrows indicate nucleus and red arrows indicate thin long cytoplasmic extensions of telocytes (telepods).

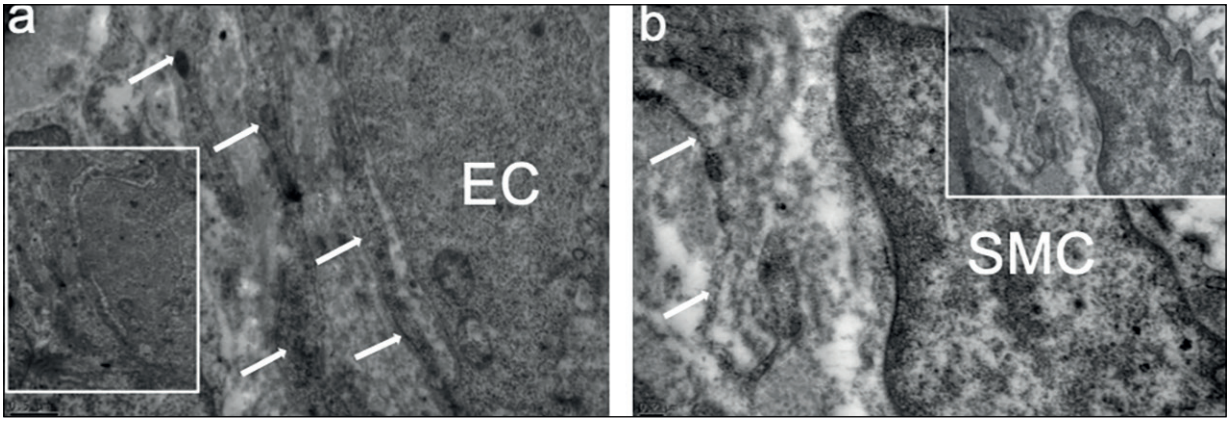

Figure 2. Ultrastructural evaluation of telocytes in EP group. **a,** Telocytes with telopods (*white arrows*) exhibited close contact with endothelial cells (EC) of capillaries. **b,** Telocytes located between smooth cells (SMC).

maximum contraction response was also higher in the EP group *(p*<0.001) (Table II).

The cumulative oxytocin dose-contraction curves were similar at all concentrations between the groups (*p>0.05*). However, the cumulative progesterone dose-relaxation curves were significantly different between the groups, with a higher relaxation response in the EP group at all concentrations (*p*<0.001). The difference between two groups was more prominent at lower doses and curves were approximated at higher doses (Figure 5).

The half maximal effective concentration (EC50) for oxytocin was higher in the EP group (0.36 M *vs*. 0.51 M) *(p*<0.001). The half inhibitory concentration (IC50) value for progesterone was higher in the control group (0.38 M *vs*. 0.22 M) (*p*<0.001).

Discussion

In the present study, we evaluated the number of telocytes in the fallopian tubes obtained from EP and control patients using different immunohistochemical antibodies. The total number of telocytes increased in the muscular layer and serosa for all the antigens stained in the EP group. *In vitro* experiments comparing tubal muscular activity revealed slower frequency of spontaneous contractions and higher amplitude of contractions in ectopic pregnancies. Although the oxytocin response was similar, the relaxation response to progesterone was higher in the EP group, suggesting modulation of the tubal function by telocytes.

To the best of our knowledge, this is the first study to investigate the role of telocytes in the pathophysiology of EP by immunohistochemical phenotyping and functional physiological experiments. In previous studies, telocytes were reported to be capable of controlling the muscular activity in the genital system due to their cell structures, localization, intercellular relationships, expressed steroid receptors and numerous potassium, chloride and calcium channels[11-15]. Telocytes are in connection with various structures such as smooth muscle cells, nerve terminals, blood vessels, progenitor cells and immune cells[16,17]. They can be a part and regulator of a bioelectrical network. It has been suggested that any disturbance of this three-dimensional network may cause impairment in the intercellular signaling resulting in some degree of dysfunction[16,17]. However, it still remains unclear whether these connections initiate the same type of response in every smooth muscle and the effect of telocytes on the control of muscular activity is controversial. In contrast to the previous manuscripts regarding a wide range of telocytes functions involved in bioelectrical activity, pacemaking and motility/contractility regulation[18,19], Roatesi et al[20] reported that uterine telocytes did not have a pacemaker activity and it was not essential since a continuous peristaltic activity was not required in the uterus. This statement is not completely true. There is regular peristaltic activity in the uterus and fallopian tube that takes part in menstrual, tubal functions and fertility[21,22]. Modulation of muscular activity can also be achieved in an inhibitory way. Duquette et al[15] stated that ICC like cells in uterine tissue samples were not pacemakers or slow wave generators supported by their voltage-clamp experiments revealing an outward current, but no inward current. The au-

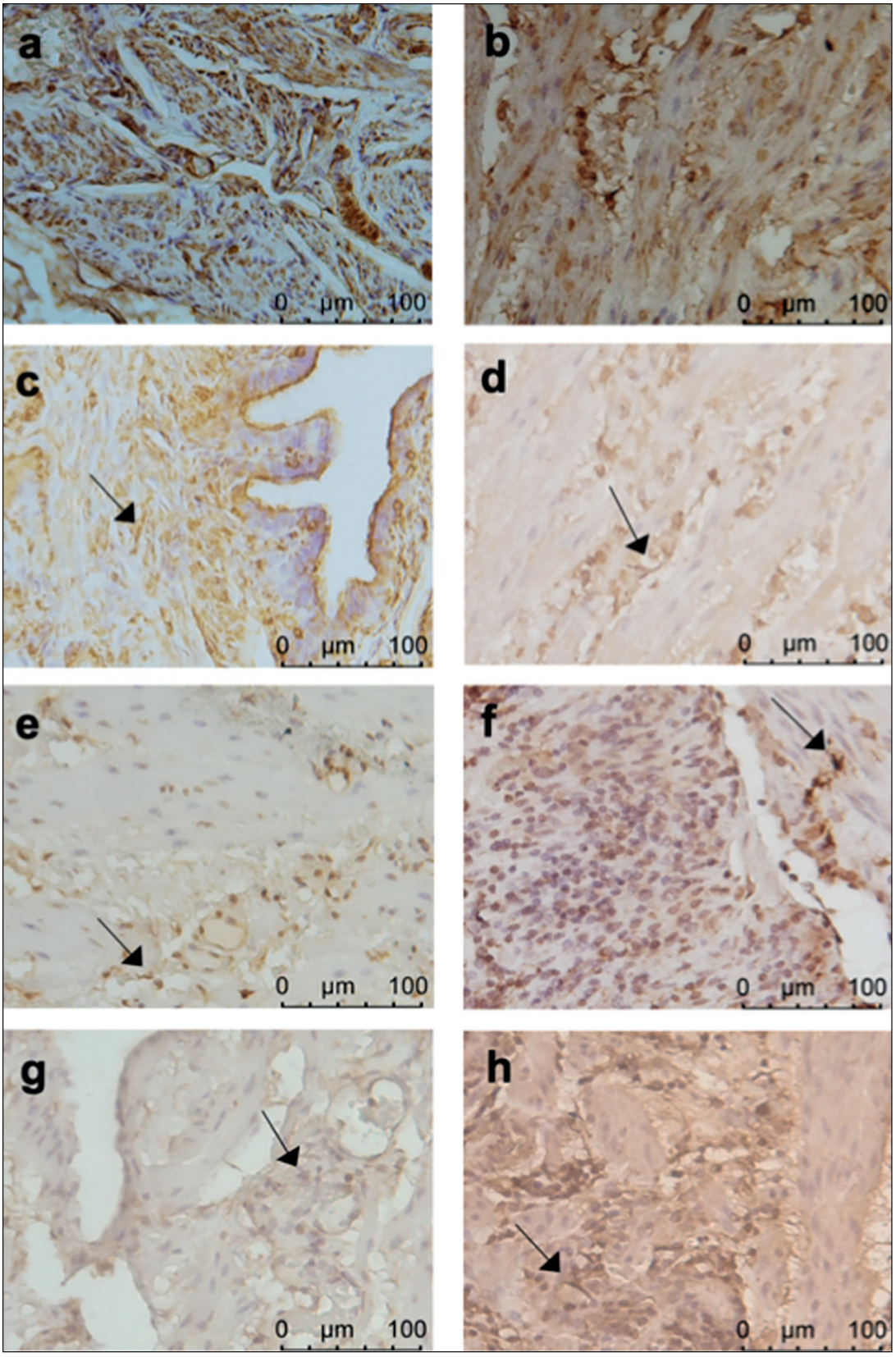

Figure 3. Immunohistochemical staining for vimentin, S100A, c-Kit, CD34 in fallopian tubes in control and EP groups. **a, b,** vimentin; **c, d,** S100A; **e, f,** C-Kit; **g, h,** CD34 stainings. Arrows indicate telocytes (40×), counterstained with haematoxylin.

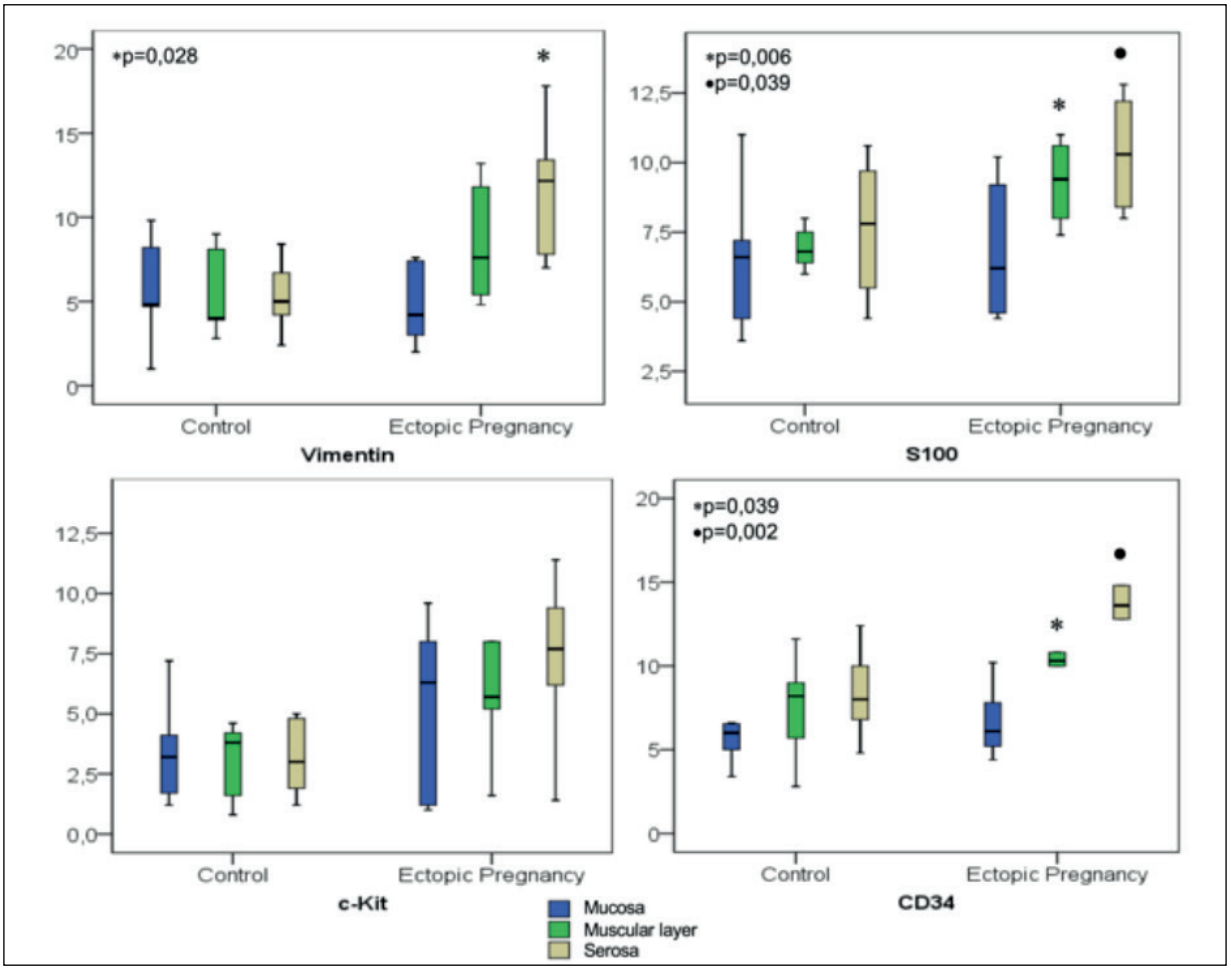

Figure 4. Number of telocytes in the mucosa, muscular layer and serosa of the fallopian tubes in the control and the EP groups.

thors concluded that intrinsic activity of the uterus is the characteristic of smooth muscle cells, while telocytes may have an inhibitory activity. In our study, the decrease in the frequency spontaneous contraction in EP can be attributed to the inhibitory effect of increased number of telocytes. Although the cell membrane potentials of telocytes have not been investigated in our study, the increased telocyte number and decreased spontaneous contraction frequency in EP supports this finding. Undoubtedly, this is an indirect assumption and should be confirmed in further studies. On the other hand, the higher contraction amplitudes in EP can be attributed to an increase in the amount of cytoplasmic calcium due to the decreased contraction frequency.

Steroid hormones affect fallopian tube functions through many mechanisms. Progesterone receptors are found both in the mucosal epithelial cells and smooth muscle cells. Progesterone also reduces ciliary movements and smooth muscle peristalsis directly and indirectly by affecting

Table II. Spontaneous and KCl-induced contraction responses in Control and Ectopic Pregnancy Groups.

		Control (n = 10)	Ectopic pregnancy (n = 10)	*p*-value
Spontaneous Contraction	Frequency (Hertz)	6.20 (4.90-7.30)	3.60 (2.20-4.50)	< 0.001*
	Amplitude (mg/g wet tissue)	0.975 (0.79-1.25)	1.98 (1.20-2.41)	< 0.001*
KCl-Induced Contraction	Amplitude (mg/g wet tissue)	2.29 (1.80-2.80)	3.45 (2.60-3.88)	< 0.001*

Values are given as median (min-max). *Mann-Whitney U test.

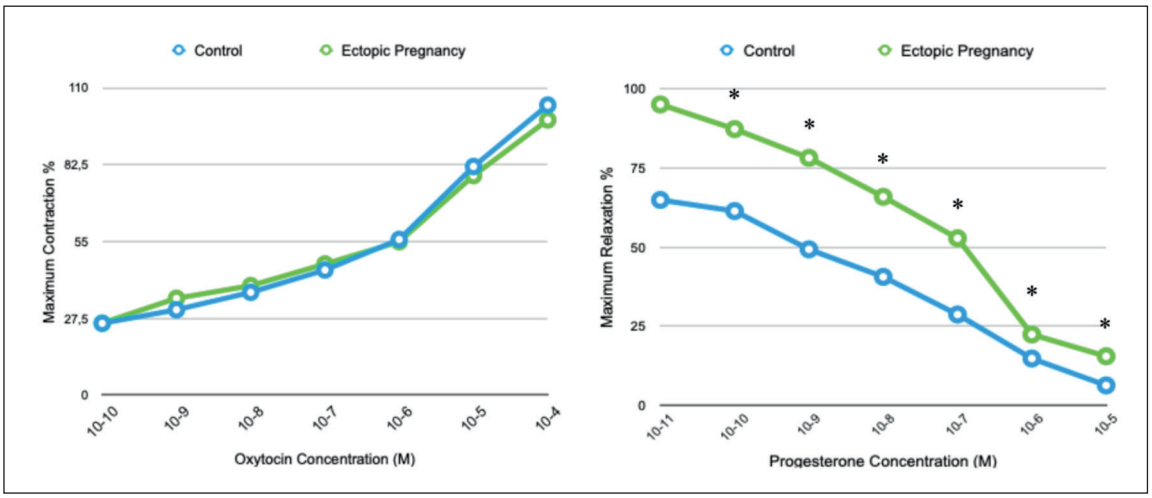

Figure 5. Cumulative oxytocin and progesterone response of the fallopian tube in control and EP patients. *$p<0.001$.

the synthesis of prostaglandins, endothelin and nitric oxide[23]. This inhibitory function affects the transfer of the cumulus oophorus complex and blastocyst to the uterine cavity. Modulation of myogenic function by steroid hormones is likely to involve telocytes either directly affecting smooth muscle cells or indirectly by transferring biomolecules[7,21,24]. Telocytes have been shown to express progesterone receptors. Cretoiu et al[25] reported that progesterone reduced tubal peristaltic activity via telocytes. In our study, in the EP group the relaxation response to the progesterone was higher, specifically at lower doses. We believe that the increased telocyte number promotes the inhibitory effect of progesterone, which elevates after fertilization, by reducing the tubal motility, thereby preventing the blastocyst from reaching the uterine cavity and may play a role in the pathogenesis EP.

Oxytocin also plays an important role in the control of spontaneous and evoked muscular activity in the fallopian tube, a critical component for transport of the gametes and embryo. Oxytocin is an agonist causing smooth muscle contraction, being specifically important in the genital system. Although the contractile effect of oxytocin in the uterus is clear, controversial results have been reported for the fallopian tube[26,27]. Jankovic et al[26] reported that oxytocin caused a relaxation response in histamine-contracted tubal tissue. Wanggren et al[27] also showed that oxytocin administration caused relaxation response following a short contraction. On the other hand, Guiloff et al[28] reported that oxytocin caused dose-dependent contractions in the fallopian. In our study, we observed an increased contraction response as the oxytocin dose increased in both groups. Kazaryan et al[29] also reported that spontaneous electrical activity was prolonged and the spike frequency increased at high oxytocin doses *in situ*. The authors attributed this effect to the increased density of ICC-like cells in the fallopian tube. Furthermore, an increasing oxytocin receptor expression from the beginning of pregnancy was shown to contribute to a higher contractile effect of oxytocin[30]. Since oxytocin was reported to increase T-type calcium channels on telocytes, the resulting change in the intracellular calcium concentration may initiate various cascades modulating the smooth muscle function[24,31].

There is a need for other studies investigating the role of telocyte dysfunction in tubal functions and pathogenesis of EP. It should be considered that the increased number of telocytes in EP may be a result rather than a cause. There are controversial results regarding the effects of inflammation on telocytes. Telocytes increase in size and number in the regeneration process after tissue damage and may play a role in cardiac regeneration[32,33]. In contrast, the reduced number of tubal telocytes and attenuated tubal functions was shown in acute salpingitis and endometriosis[34,35]. In our study, we showed increased number of telocytes in EP. Telocytes have complex protein synthesis mechanisms and can change cellular gene expression processes epigenetically and provide regeneration in their cellular network, that may end up with altered functional interactions[33,36]. Nevertheless, the increase in the

number of telocytes in our study suggests that tubal dysfunction associated with the increase in telocyte number may contribute to the pathogenesis of EP.

Conclusions

The unique cell population, telocytes, are associated with contractility of the smooth muscle layer and alterations in number may play an important role in the pathogenesis of EP. Increased telocyte count in the fallopian tube may decrease tubal motility and may affect the transfer of the blastocyst to the uterus. Further researches are necessary focusing on telocytes and their role in EP and other fallopian tube pathologies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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References

1) Bouyer J, Coste J, Fernandez H, Pouly JL, Job-Spira N. Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. Hum Reprod 2002; 17: 3224-3330.
2) Shaw JL, Dey SK, Critchley HO, Horne AW. Current knowledge of the aetiology of human tubal ectopic pregnancy. Hum Reprod Update 2010; 16: 432-444.
3) Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, Job-Spira N. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol 2003; 157: 185-194.
4) Dixon RE, Hwang SJ, Kim BH, Sanders KM, Ward SM. Myosalpinx Contractions Are Essential for Egg Transport Along the Oviduct and Are Disrupted in Reproductive Tract Diseases. Adv Exp Med Biol 2019; 1124: 265-294.
5) Edelstein L, Smythies J. The role of telocytes in morphogenetic bioelectrical signaling: once more unto the breach. Front Mol Neurosci 2014; 7: 41.
6) Zheng Y, Bai C, Wang X. Telocyte morphologies and potential roles in diseases. J Cell Physiol 2012; 227: 2311-2317.
7) Urban L, Miko M, Kajanova M, Bozikova S, Mrazova H, Varga I. Telocytes (interstitial Cajal-like cells) in human Fallopian tubes. Bratisl Lek Listy 2016; 117: 263-267.
8) Shafik A, Shafik AA, El Sibai O, Shafik IA. Specialized pacemaking cells in the human Fallopian tube. Mol Hum Reprod 2005; 11: 503-505.
9) Ciontea SM, Radu E, Regalia T, Ceafalan L, Cretoiu D, Gherghiceanu M, Braga RI, Malincenco M, Zagrean L, Hinescu ME, Popescu LM. C-kit immunopositive interstitial cells (Cajal-type) in human myometrium. J Cell Mol Med 2005; 9: 407-420.
10) Stulberg DB, Cain L, Dahlquist IH, Lauderdale DS. Ectopic pregnancy morbidity and mortality in low-income women, 2004-2008. Hum Reprod 2016; 31: 666-671.
11) Shafik A, El-Sibai O, Shafik I, Shafik AA. Immunohistochemical identification of the pacemaker cajal cells in the normal human vagina. Arch Gynecol Obstet 2005; 272: 13-16.
12) Cretoiu D, Ciontea SM, Popescu LM, Ceafalan L, Ardeleanu C. Interstitial Cajal-like cells (ICLC) as steroid hormone sensors in human myometrium: immunocytochemical approach. J Cell Mol Med 2006; 10: 789-795.
13) Popescu LM, Ciontea SM, Cretoiu D. Interstitial Cajal-like cells in human uterus and fallopian tube. Ann N Y Acad Sci 2007; 1101: 139-165.
14) Banciu A, Banciu DD, Mustaciosu CC, Radu M, Cretoiu D, Xiao J, et al. Beta-Estradiol Regulates Voltage-Gated Calcium Channels and Estrogen Receptors in Telocytes from Human Myometrium. Int J Mol Sci 2018; 19.
15) Duquette RA, Shmygol A, Vaillant C, Mobasheri A, Pope M, Burdyga T, Wray S. Vimentin-positive, c-kit-negative interstitial cells in human and rat uterus: a role in pacemaking? Biol Reprod 2005; 72: 276-283.
16) Manetti M, Guiducci S, Ruffo M, Rosa I, Faussone-Pellegrini MS, Matucci-Cerinic M, Ibba-Manneschi L. Evidence for progressive reduction and loss of telocytes in the dermal cellular network of systemic sclerosis. J Cell Mol Med 2013; 17: 482-496.
17) Manetti M, Rosa I, Messerini L, Guiducci S, Matucci-Cerinic M, Ibba-Manneschi L. A loss of telocytes accompanies fibrosis of multiple organs in systemic sclerosis. J Cell Mol Med 2014; 18: 253-262.
18) Varga I, Polak S, Kyselovic J, Kachlik D, Danisovic L, Klein M. Recently Discovered Interstitial Cell Population of Telocytes: Distinguishing Facts from Fiction Regarding Their Role in the Pathogenesis of Diverse Diseases Called "Telocytopathies". Medicina (Kaunas) 2019; 55.
19) Shim W. Myocardial Telocytes: A New Player in Electric Circuitry of the Heart. Adv Exp Med Biol 2016; 913: 241-251.
20) Roatesi I, Radu BM, Cretoiu D, Cretoiu SM. Uterine Telocytes: A Review of Current Knowledge. Biol Reprod 2015; 93: 10.
21) Kunz G, Leyendecker G. Uterine peristaltic activity during the menstrual cycle: characteriza-

tion, regulation, function and dysfunction. Reprod Biomed Online 2002; 4 Suppl 3: 5-9.

22) Leyendecker G, Kunz G, Wildt L, Beil D, Deininger H. Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. Hum Reprod 1996; 11: 1542-1551.

23) Bylander A, Gunnarsson L, Shao R, Billig H, Larsson DG. Progesterone-mediated effects on gene expression and oocyte-cumulus complex transport in the mouse fallopian tube. Reprod Biol Endocrinol 2015; 13: 40.

24) Hutchings G, Williams O, Cretoiu D, Ciontea SM. Myometrial interstitial cells and the coordination of myometrial contractility. J Cell Mol Med 2009; 13: 4268-4282.

25) Cretoiu SM, Cretoiu D, Marin A, Radu BM, Popescu LM. Telocytes: ultrastructural, immunohistochemical and electrophysiological characteristics in human myometrium. Reproduction 2013; 145: 357-370.

26) Jankovic SM, Varjacic M, Protic B. Relaxant effect of oxytocin on isolated human oviduct. Croat Med J 2001; 42: 511-516.

27) Wanggren K, Stavreus-Evers A, Olsson C, Andersson E, Gemzell-Danielsson K. Regulation of muscular contractions in the human Fallopian tube through prostaglandins and progestagens. Hum Reprod 2008; 23: 2359-2368.

28) Guiloff E, Ibarra-Polo AA, Gomez-Rogers C. Effect of oxytocin on the contractility of the human oviduct in vivo. Fertil Steril 1974; 25: 946-953.

29) Kazarian KV, Unanian NG, Meliksetian IB, Akopian RR, Saakian AA. [Role of oxytocin in activation of spontaneous electrical activity of uterine body and uterine tubes in non-pregnant rats]. Zh Evol Biokhim Fiziol 2011; 47: 239-245.

30) Robinson RS, Mann GE, Lamming GE, Wathes DC. The effect of pregnancy on the expression of uterine oxytocin, oestrogen and progesterone receptors during early pregnancy in the cow. J Endocrinol 1999; 160: 21-33.

31) Aleksandrovych V, Walocha JA, Gil K. Telocytes in female reproductive system (human and animal). J Cell Mol Med 2016; 20: 994-1000.

32) Diaz-Flores L, Gutierrez R, Gonzalez-Gomez M, Diaz-Flores L, Jr., Valladares F, Rancel N, et al. Telocyte Behaviour During Inflammation, Repair and Tumour Stroma Formation. Adv Exp Med Biol 2016; 913: 177-191.

33) Bei Y, Zhou Q, Sun Q, Xiao J. Telocytes in cardiac regeneration and repair. Semin Cell Dev Biol 2016; 55: 14-21.

34) Yang J, Chi C, Liu Z, Yang G, Shen ZJ, Yang XJ. Ultrastructure damage of oviduct telocytes in rat model of acute salpingitis. J Cell Mol Med 2015; 19: 1720-1728.

35) Yang XJ, Yang J, Liu Z, Yang G, Shen ZJ. Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility. J Cell Mol Med 2015; 19: 452-462.

36) Chaitow L. Telocytes: Connective tissue repair and communication cells. J Bodyw Mov Ther 2017; 21: 231-233.