IJVAR *International Journal of Veterinary and Animal Research*
Uluslararası Veteriner ve Hayvan Araştırmaları Dergisi
E-ISSN: 2651-3609 2(2): 46-50, 2019

The Effect of Gamithromycin on Smooth Muscle of Rat Uterus *In Vitro*

Tolga Trak[1], Ebru Yıldırım[2*], Begüm Yurdakok-Dikmen[3]

[1]Kalecik District Directorate of Agriculture and Forestry, Kalecik, Ankara
[2]Kırıkkale University, Veterinary Faculty, Department of Pharmacology and Toxicology, Yahşihan, Kırıkkale
[3]Ankara University, Veterinary Faculty, Department of Pharmacology and Toxicology, Dışkapı, Ankara

*Corresponding Author

E-mail:ebruyildirim@kku.edu.tr

Received: November 13, 2019

Accepted: December 03, 2019

Abstract
The purpose of this study was to investigate the effect of gamithromycin on rat uterus smooth muscles and to evaluate the possible mechanism of action. Forty-four uterine tissues isolated from 16 female Wistar rats weighing 200-250 grams were used in the experiments. In the preliminary experiments, gamithromycin was tested at concentrations of 10^{-7} M, 10^{-6} M and 10^{-5} M; where 10^{-5} M was selected for the experiments. In Group 1, the uterus segments were treated for 10 min with 10^{-5} M gamithromycin following 10 min control contractions. In Group 2, the effect of 10^{-5} M gamithromycin over 2.5 mIU / mL oxytocin contraction was evaluated. In Group 3, the effect of 10^{-5} M gamithromycin was evaluated over 10^{-8} M atropine incubation. In Group 4, 10^{-5} M gamithromycin was applied for 10 min followed by 0.0625 µg/ml of cloprostenol application. The same protocols were applied for dimethylsulfoxide (DMSO) as control. Frequency, average amplitude and peak amplitude values of the contractions were assessed. In Group 1, gamithromycin in were shown to increase the contractility at 10^{-5} M significantly ($p=0.01$); while no statistically significant difference was observed in comparison to DMSO ($p> 0.05$). For the other tested groups, no statistically important difference were observed ($p> 0.05$). The nonsignificant difference of the results of this study can be attributed to the chemical form of gamithromycin and the concentration used. In order to be able to fully assess the effects and possible mechanism of gamihtromycin on the uterine smooth muscle, higher or different gamithromycin concentrations should be studied and, if possible, further studies should be performed with different agonist and antagonist agents.

Keywords: Gamithromycin, *in vitro*, oxytocin, rat, uterus smooth muscle.

INTRODUCTION

Macrolid antibiotics are one of the most commonly used drugs among antibiotics. Many derivatives have been used to exhibit a high level of activity against bacterial resistance by widening the spectrum of action and extending the duration of drug activity. However there are also some rare side effects of macrolide antibiotics. These side efects include vomiting, abdominal pain and abdominal cramps, prolongation of QT interval appearing on electrocardiography, and problems related to the inhibition of drug metabolism. The most important side effects of macrolides are the effects on the gastrointestinal system which are thought to be related to the stimulation of motilin receptors, the proarrhythmic acti- on (more frequent occurrence of pre-existing arrhythmias) due to the blockage of HERG + channels, and the inhibiti- on of drug metabolism due to cytochrome P450 inhibition (Abu- Gharbieh et al. 2004).

Along with the side effects mentioned, macrolides have been used extensively in veterinary practice for a long time due to their antibacterial activity as well as their antifungal, antiparasitic and anti-inflammatory properties. New synthesized members are added to this group every year. Gamithromycin is a macrolide group antibiotic belonging to the 16-member semi-synthetic azalide subclass. The lactone ring has an alkylated nitrogen atom at position 7a. Gamithromycin azalide group is used in the treatment and prevention of respiratory diseases of cattle (Kellermann et al. 2014); licensed as Zactran® (Watteyn et al. 2013). Zactran® is a licenced drug in European countries (EMA, 2019) and Turkey (Anonym, 2019). This drug is allowed to be used in cattle pig and sheep (EMA, 2019) However, gamithromycin is expected to find potential applications on other animals in veterinary practice; as supported by the researches in chic- ken (Watteyn et al. 2013) and foals (Berghaus et al. 2012).

Antibiotic drugs are commonly used against bacterial diseases because of their effects on bacteria. However, the systemic effects of the antibiotics in the animals should not be ignored (Picinno et al. 2014). For example, erythromycin has been shown to produce increased motility similar to normal gastrointestinal tract motor activity in the gastrointestinal tract (Omura et al. 1987). Itoh et al. (1984) showed the strong motor activity of erythromycin on isolated canine stomach, duodenum and upper jejenum isolated tissues. Again, in a study conducted on human isolated bronchus erythromycin, roxithromycin, clarithromycin have been shown to prevent neural contractions (Tamaoki et al. 1995).

Other than their antibacterial effects, antibiotics can show pharmacological effects of on uterus (Picinno et al. 2014). Uterine contractions play a key role in many reproductive events like transport of sperm and embryo, pregnancy and birth (Otaibi, 2014). Uterus is vital in both prenatal and postnatal periods. Hormonal, neural and metabolic activities, neuromediators, ion channels and intracellular signaling systems play a role in the regulation of uterine smooth muscle activity (Aguilar and Mitchell 2010). Although there are pharmacokinetic studies on gamithromycin, and pharmacodynamic studies for other macrolide antibiotics, no studies are present for determining its effect on uterine muscle contractions *in vitro.* The detection of other possible effects of gamithromycin, a new generation macrolide, would be of great benefit in the veterinary field. On the other hand, the changes in the uterine contractions due to drugs is very important, in terms of obstetrics practice, because this may disrupt the normal course of labor (Adebiyi et al. 2004). Therefore this study was designed to evaluate the effects of gamithromycin on uterine contractions *in vitro*; which will eventually contribute to the assessment of possible side effects.

MATERIALS AND METHODS

Experimental animals

Forty four uterine tissues isolated from 16 Wistar albino female rats weighing 200-250 grams (g) were used in the experiments. The female rats were kept in the same cage for 12 hours under light, 12 hours under dark without any restriction on feed and water. Four animals were kept in each cage. All animals were examined at the Hüseyin Aytemiz Experimental Research and Application Center of Kırıkkale University University during the experiment. The study was approved by Kirikkale University University Animal Experiments Local Ethics Committee dated 22.06.2018, decision number 18/06, meeting number 34.

Drugs and solutions

Gamithromycin (Vetranal, Sigma 32161): Disolved with Dimethyl sulfoxide (DMSO), and stored as 10^{-3} M concentration stock. Dimethylsulfoxide (Ambresco, 0231). Oxytocin (Vetaş). Atropine sulfate monohydrate (Chem Cruz, sc- 203322). Cloprostenol sodium (Estrumate, Vetas). Ketamine (Ketalar, Pfizer). Xylazine (Rompun, Bayer) Dale solution: NaCl 154 mM, KCl 5.63 mM, $NaHCO_3$ 5.95 mM, $CaCl_2$ 1.63 mM, $MgCl_2$ 0.024 mM and dextrose 2.77 mM

The isolation of rat uterus

Rats were anesthetized by intraperitoneal (ip) ketamine (50 mg / kg) and xylazine (10 mg / kg). When the rats were anesthetized, the anterior abdominal wall was opened and uterine tissue was removed. The uterus was isolated and suspended in the isolated organ bath (Biopac system, MP35, Commat, Turkey) with 10 mL of Dale solution by 1 g of pretension. In the study, the temperature of the organ baths was adjusted to 37 °C and viability was maintained with a mixture of 95% O_2 and 5% CO_2 gas and pH 7.4 throughout the experiment.

Study Protocols

The tissues were exposed to a 30 minutes of equilibration period, during this period the Dale's solution was changed at 15 minute intervals.

Preliminary study was conducted for the determination of the gamithromycin concentration to be further used in experiments. Preliminary experiments were performed on 8 isolated uterine preparations obtained from 3 animals using 10^{-7}-10^{-5}M gamithromycin. The results from the preliminary studies revealed no difference in the amplitude and frequency of uterine contractions; therefore, the protocols were carried out using the highest concentration of gamithromycin as 10^{-5}M.

Group 1 (Protocol 1): Spontaneous contractions were measured for 10 min after a 30 min equilibration period. After changing Dale's solution 3 times at 5 min intervals, DMSO was applied for 10 min. The solution in the bath was changed again and spontaneous contraction process was started for 10 min. Washing was performed at the end of the period and 10^{-5} M gamithromycin was applied for 10 minutes.

Group 2 (Protocol 2): After 30 min. of equilibration period, oxytocin (2.5 mIU / mL) was administered for 10 min (Öcal et al. 2004), and DMSO was applied for 10 min. without changing the Dale's solution. The tissues were washed 3 or 4 times with 5 min intervals and then for 10 min (2.5 mIU/mL) oxytocin was applied. 10^{-5} M gamithromycin was applied for 10 min afterwards.

Group 3 (Protocol 3): After 30 min. of equilibration period, 10^{-8}M (Martinez Mir, 2002) atropine was applied for 10 min. and DMSO was applied for 10 min. without washing. Dale' s solution was changed 3 or 4 times at 5 min intervals and then for 10 min 10^{-8} M atropine for 10 min and 10^{-5} M gamithromycin was applied for 10 min

Group 4 (Protocol 4): Thirty min. after the equilibration period, 0.0625 µg/ml cloprostenol was applied for 10 min. Following incubation, DMSO was applied for 10 min. Da- le's solution was changed 3 times with 5 minutes intervals. Soon the tissues returned to normal contractions, 0.0625 µg/ ml cloprostenol was applied for 10 min. Following incubati- on, 10^{-5}M gamithromycin was applied for 10 min.

To evaluate the data, frequency and the amplitude of the contractions were calculated. The frequency was determined by counting the peaks of all contractions occurring in 10 min. When calculating the average amplitude; all contractions formed according to the baseline in 10 min time period (amplitudes were found by subtracting the value of baseline from the value of highest contraction) were averaged one by one. Peak amplitude was calculated by taking the value of the highest contraction according to the baseline in the 10 min period. These values were determined in mg.

Statistical analysis

Statistical calculations were performed using the SPSS 15 for Windows statistical package program. Data of the study were given as arithmetic mean and standard error. First of all, normality test was performed. Paired t test was used between the two groups with parametric data and for nonparametric data, Wilcoxon Signed Ranks test was used. $P < 0.05$ was considered statistically significant.

RESULTS

According to the first protocol findings of the study, the frequency value of spontaneous contractions (Control) (8.60 ± 0.75) and the frequency of DMSO application (7.60 ± 0.58) were not statistically significant ($p > 0.05$); The frequency of gamitromycin (10^{-5}M) (7.70 ± 0.63) was statistically higher than the frequency of spontaneous contractions (7.00 ± 0.58) ($p=0.01$). However, when the frequencies of DMSO and 10^{-5} M gamithromycin application was com- pared, no statistically significant difference was found ($p > 0.05$) (Table 1). When the other parameters were compared, no difference was found. In Table 1. the frequency (number), mean amplitude (mg) and peak amplitude (mg) values of contractions obtained from Protocol 1 are given.

Table 1. The frequency (number), mean amplitude (mg), and peak amplitude (mg) of contractions obtained from protocol 1

Parameters	Control	DMSO	p	Control	Gamit	p
Frequency	8.60±0.75	7.60±0.58	0.16	7.00±0.58	7.70±0.63**	0.01
Mean amplitude	4025.41±879.75	3730.79±825.65	0.21	3477.47±842.34	3388.90±835.49	0.29
Peak amplitude	4448.44±888.85	4270.78±865.63	0.35	3985.91±835.41	4052.04±835.94	0.60

DMSO: Dimethylsulfoxide), Gamit: Gamithromycin. ** The difference between the frequency of gamitromycin administration and the frequency (number) of the control is significant ($p=0.01$). There was no difference between DMSO and Gamithromycin in terms of frequency values ($p> 0.05$). In addition, there was no difference between the mean amplitude (mg) and peak ampli- tude (mg) values between the groups ($p> 0.05$). n: 10 (n: number of uterine tissue).

No differences were found between the data obtained from protocols 2, 3 and 4. (Tables 2, 3 and 4).

Table 2. The frequency (number), mean amplitude (mg), and peak amplitude (mg) of contractions obtained from protocol 2

Parameters	Oxytocin	Oxytocin+ DMSO	p	Oxytocin	Oxytocin+ Gamit	p
Frequency	15.42±0.65	13.67±0.66	0.06	13.92±0.56	13.08±0.77	0.13
Mean amplitude	4910.42±645.77	4918.19±602.73	0.93	4341.75±663.42	4889.03±621.70	0.08
Peak amplitude	5873.21±655.66	5681.73±584.92	0.14	5258.14±660.47	5445.92±581.15	0.24

(n: 12) (n: number of uterus)

Table 3. The frequency (number), mean amplitude (mg), and peak amplitude (mg) of contractions obtained from protocol 3

Parameters	Atropine	Atropine+ DMSO	p	Atropine	Atropine+ Gamit	p
Frequency	11.43±2.60	11.71±2.43	0.65	8.86±2.12	8.57±2.19	0.36
Mean amplitude	4196.06±960.08	4014.06±966.27	0.45	4110.31±924.36	4108.63±929.88	0.98
Peak amplitude	4654.50±907.87	4326.86±917.92	0.21	4499.50±850.76	4394.50±876.75	0.52

(n: 7), (n: number of uterus)

Table 4. The frequency (number), mean amplitude (mg), and peak amplitude (mg) of contractions obtained from protocol

Parameters	Cloprostenol	Cloprostenol+ DMSO	p	Cloprostenol	Cloprostenol +Gamit	p
Frequency	17.14±1.06	17.57±1.09	0.51	16.14±1.14	16.43±1.09	0.52
Mean amplitude	4343.50±609.43	4400.57±762.72	0.85	4467.79±733.95	4394.14±709.42	0.48
Peak amplitude	5330.91±745.59	5026.20±864.25	0.20	5125.51±804.82	5087.90±782.43	0.27

(n: 7) (n: number of uterus)

DISCUSSION AND CONCLUSION

In addition to the antimicrobial effects of macrolide antibiotics, there are many pharmacodynamic effects, such as antiinflammatory effect, immune system regulations and prokinetic effects in the gastrointestinal tract. (Hawkyard and Koerner, 2007).

In a study investigating the relationship between interdigestive contractions and the chemical structure of macrolides in the dog's gastrointestinal tract, it is found that 14 membered erythromycin and oleandomycin which have glycoside linkage in the lactone ring, formed gastrointestinal contractions together with the release of endogenous motilin, while 16 membered leukomycin, acetylspiramin, and acetylspiramycin did cause neither motile release nor contractions. The results of the mentioned study suggested that the intestinal contractions produced by macrolides are related to the chemical structure of macrolide antibiotics (Itoh et al. 1985).

Some macrolide antibiotics also have a relaxing effect on bronchial smooth muscles. Daenas et al. (2006) studied the effect of azithromycin, on tissues precontracted with potassium chloride and carbachol in rabbit trachea smooth muscles and found the relaxant effects of azithromycin. This relaxation in the muscles did not change in the presence of atropine or epithelial removel of the tissue. Nissan et al. (1999) stated that erythromycin had an inhibitory effect on rat urinary bladder. Karaca and İnce (2016) showed that 10^{-3} M erythromycin decreases the response of contractions in- duced by carbocol and KCl in the isolated urinary bladder of rats; this inhibitory effect was more pronounced in rats with hyperthyroidism.

Çelik et al. (2001) investigated the effect of erythromycin in human pregnant myometrium, and found that 10^{-1}, $2x10^{-1}$, $5x10^{-1}$ and 1 mM erythromycin decreased peak amplitude and decreased frequencies depending on concentration. The authors emphasized that erythromycin may have beneficial effects on infection related premature birth cases, but further studies are needed to elucidate the usefulness of erythromycin as a tocolytic agent. In the present study, although 10^{-5}M gamitromycin increased the frequency value ($p=0.01$), no difference has been recorded between the frequency of DMSO and gamithromycin. There was no difference in mean amplitude and peak amplitude values ($p>0.05$). This may be due to the different concentrations of gamitromycin or the chemical structure of gamithromycin. In fact, it was emphasized that contractions formed in the intestine by macrolides are related to the chemical structure of macrolide antibiotics (Itoh et al. 1984).

In a study conducted by Granovsky-Grisaru et al. (1998) erythromycin has shown to reduce phasic contractions induced by oxytocin and carbocol in rat pregnant myometrium. This effect of erythromycin started at 0.01 mmol / L erythromycine. At 1 mmol / L, the contractions decreased the amplitudes by 22% and the frequencies by 38%. These findings were not consistent with the findings of the present study; In this study, the frequency and amplitude values of 10^{-5} M gamithromycin on 2.5 mIU / mL oxytocin induced contractions of rat uterus did not change ($P > 0.05$). This may be due to the fact that the responses of the pregnant uterus and the nonpregnant uterus or the concentration of gamithromycine used in the present study.

Mehrdad et al. (2011) investigated the effect of tulatromycin, in oxytocin and KCl-induced contractions at rat concentrations of 1, 2, 4, 8, 16 mmol; found that the contractions of uterine smooth muscles are inhibited depending on the concentration.

Prostaglandins (PGs) affect ovarian, uterus, placental and pituitary functions to regulate reproduction in female animals. They play an important role in ovulation, luteal function, maternal recognition of pregnancy, implantation, maintenance of pregnancy, microbial miscarriages, birth, postnatal uterus and ovarian infections and postnatal ovarian cycles (Weems et al. 2006). Sharif (2008) studied PG anologues including PGF2α and cloprostenol in rat uterus *in vitro*. They have shown that FP (Prostaglandin F) receptors are sti- mulated by these anologues. the present study, cloprostenol increased the contractions of the rat uterus.

In a study investigating the effect of erythromycin in the rat uterus, 10^{-5} M erythromycin was found to be ineffective, but the inhibitory effects started from 10^{-4} M. 0.1, 0.2, 0.5 and 1 mM erythromycin reduced the frequency and amplitude of $PGF_{2\alpha}$-induced contractions. Since $PGF_{2\alpha}$ induced contractions are important in the pathogenesis of primary dysmonorrhea in humans, researchers have stated that erythromycin may contribute to treatment in this respect (Çelik et al. 2002). A macrolide antibiotic clarithromycin had shown to reduce the amplitude value of uterine contractions induced by 800 mU / L oxytocin, 1 µM PGF2α and 30 mM KCl in human myometrium (Çelik and Ayar, 2002). Çelik and Ayar (2002) also stated that this inhibitory effect was due to the concentration of erithromycin as no change was seen at 10^{4} M; where the inhibitory effect starts at 0.2 mM concentration. In a study conducted in the gut of the dog, it was shown that atropine sulfate prevents erythromycin and oleandomycin induced contractions (Itoh et al.1984). In the present study, atropine incubation did not alter the effect of 10^{-5} M gamithromycin.

To sum up, the findings of our study indicate that 10^{-5} M gamithromycine caused no contractile effect with no significant change in frequency and tension on rat uterine smooth muscle *in vitro*. These results were thought to be dependent on the chemical structure of gamithromycin (15 membered macrolide) and concentration used. Further studies on hig- her or different concentrations and on different target species will allow gain sights of its effects on uterus.

REFERENCES

Abu-Gharbieh E, Vasina V, Poluzzi E, De Ponti F. 2004. Antibacterial macrolides: a drug class with a complex pharmacological profile. Pharmacol Res. 50(3):211-22.

Adebiyi A., Adaikan P.G., Prasad R.N. 2004. Effect of benzyl isothio-cyanate on spontaneous and induced force of rat uterine contraction. Pharmacol. Res., 49, 415.

Aguilar HN, Mitchell BF. 2010. Physiological pathways and molecular mechanisms regulating uterine contractility. Hum Reprod Update, 16(6): 725-44.

Anonymous. 2019. Retrieved from: https://hbs.tarbil.gov.tr/ Retrieved date: 24.11.2019

Berghaus LJ, Giguire S, Sturgill TL, Blade D, Malinski TJ, Huang R. 2012. Plazma Pharmacokinetics, pulmonary distribution, and in vitro activity of gamithromycin in foals. J Vet Pharmacol Ther, 35(1):59-66.

Berridge MJ. 2008. Smooth muscle cell calcium activation mechanisms. J Physiol, 586(21):5047-61.

Çelik H, Ayar A, Baltaci A, Tug N. 2002. Erythromycin inhibits prostaglandin F_2 α-induced contractions of myometrium isolated from non-pregnant rats, BJOG: an International Journal of Obstetrics and Gynecology, 109(9): 1036-40.

Çelik H, Ayar A, Sapmaz E. 2001. Effects of erythromycin on stretch-induced contractile activity of isolated myometrium from pregnant women. Acta Obstet Gynecol Scand, 80(8):697-701.

Çelik H, Ayar A. 2002. Clarithromycin inhibits myometrial contractions in isolated human myometrium independent of stimulus. Physiol Res. 51(3):239-45.

Daenas C, Hatziefthimiou AA, Gourgoulianis KI, Molyvdas PA. 2006. Azithromycin has a direct relaxant effect on precontracted airway smooth muscle. Eur J Pharmacol, 28;553(1-3):280-7.

EMA (2019). Retrieved from: https://www.ema. europa.eu/en/documents/product - information/zactran - epar-product-information_en.pdf. Retrieved date: 21.11.2019.

Granovsky-Grisaru S, Ilan D, Grisaru D, Lavie O, Aboulafia I, Diamant YZ, Hanani M. 1998. Effects of erythromycin on contractility of isolated myometrium from pregnant rats. Am J Obstet Gynecol, 178(1 Pt 1): 171-174.

Hawkyard CV, Koerner RJ. 2007. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. J Antimicrob Chemother, 59(3): 347-58.

Itoh Z, Suzuki T, Nakaya M, Inoue M, Arai H, Wakabayashi K. 1985. Structure activity relation among macrolide antibiotics in initiation of interdigestive migrating contractions in the canine gastrointestinal tract. Am J Physiol, 248(3 Pt 1): G320-5.

Itoh Z, Suzuki T, Nakaya M, Inoue M, Mitsuhashi S. 1984. Gastrointestinal motor-stimulating activity of macrolide antibiotics and analysis of their side effects on the canine gut. Antimicrob Agents Chemother, 26(6): 863-869.

Karaca A, İnce S. 2016. Erythromycin attenuates contractile responses of isolated urinary bladders of hyperthroid rats. Vetrinarski Arhiv 86(6): 825-839.

Kellermann M, Huang RA, Forbes AB, Rehbein S. 2014. Gamithromycin plasma and skin pharmacokinetics in sheep. Resarch in Veterinary Science, 97: 199-203

Martínez-Mir I, Gil Marqués M, Morales-Olivas FJ, Rubio-Gomis E. 2002. Characteristics of histamine tachyphylaxis in rat uterine smooth muscle. Inflamm Res. 51(12):587-93.

Mehrdad NG, Yagoob A, Saeid S, Sina S. 2011. Effects of tulathromycin (Draxxin) on contractility of isolated myometrium in rats. Middle East Journal of Scientific Research 10(4): 496-500.

Nissan A, Maudlej N, Beglaibter N, Haskel Y, Freund HR, Hanani MA. 1999. Direct inhibitory effect of erythromycin on rat urinary bladder smooth muscle. The Journal of Urology, 161(3):1006-1009.

Omura B, Tsuzuki K, Sunazuka T, Marui S, Toyoda H. 1987. Macrolides with gastrointestinal motor stimulating activity. Journal of Medical Chemistry, 30: 1941-1943.

Otaibi M A. 2014. The physiological mechanism of uterine contraction with emphasis on calcium ion. Calcium signaling, 1(2): 2373-1176.

Öcal H, Yuksel M, Ayar A. 2004. Effects of gentamicin sulfate on the contractility of myometrium isolated from non-pregnant cows. Animal Reproduction Science, 84(3-4):269-77.

Piccinno M, Rizzo A, Cariello G, Staffieri F, Sciorsci RL. 2016. Oxytocin plus antibiotics: A synergism of potentiation to enhance bovine uterine contractility. Theriogenology, 15;86(5):1203-11.

Sharif NA. 2008. Synthetic FP-prostaglandin-induced contraction of rat uterus smooth muscle in vitro. Prostaglandins Leukotrienes and Essential Fatty Acids,78(3):199-207.

Tamaoki J, Tagaya E, Sakai A, Konno K. 1995. Effects of macrolide antibiotics on neurally mediated contraction of human isolated bronchus. Journal of Allergy and Clinical Immunology, 95(4): 853-9.

Watteyn A, Plessers E, Wyns H, De Baere S, De Backer P, Croubel S. 2013. Pharmacokinetics of gamithromycin after intravenous and subcutaneus administration in broiler chickens. Poultry Science, 92: 1516-1522

Weems CW, Weems YS, Randel RD. 2006. Prostaglandins and reproduction in female farm animals. The Veterinary Journal, 171(2): 206-28.

Woodcock NA, Taylor CW, Thornton S. 2006. Prostaglandin F_2 alpha increases the sensitivity of the contractile proteins to Ca2+ in human myometrium. American Journal of Obstetrics and Gynecology,195(5): 1404-6.