



# The Efficacy of Treatment of Retained Placenta with Chlortetracycline and Oxytetracycline through Local Intrauterine Route in Dairy Cows

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**Abstract** | Cows suffered from retention of fetal membranes are at severe danger of developing puerperal metritis. Current study aimed to compare using local intrauterine application of chlortetracycline with oxytetracycline in treatment of dairy cows which suffered from retained fetal membranes considering clinical traits, milk production and prevention of puerperal metritis. Sixty-five Holstein Friesian cows suffered from retained placenta were divided into three groups. The first group (G1, n=25) was administrated 5 g of chlortetracycline through the local intrauterine route. The second group (G2, n=25) was administrated 5 g of oxytetracycline through the same route, while the third group (control group, G3, n=15) had no treatment. The results indicated that 21 cows of G1 group succeeded in expelling placenta within three days after treatment, whereas in G2, 15 cows had complete shedding of the placenta within five days post treatment. On contrary, G3 failed to completely expel the placenta within the same period. None of the cows developed puerperal metritis in G1 and G2 but 80% of control group suffered from puerperal metritis. The energy intake and milk production in G1 were significantly ( $p < 0.05$ ) higher among all the groups, while in G2 the energy intake and milk production presented a significant ( $p < 0.05$ ) decrease and the highest decrease of energy intake and milk production was in G3. Checking the time of involution of the pregnant uterine horn, time of involution of the cervix, time needed for the presence of the uterus in the pelvic cavity revealed a significant ( $p < 0.05$ ) difference in G1 when compared to G2 and G3. Vaginal discharge examination revealed that 15 cows of G1 had mucopurulent discharge which disappeared rapidly in the day 32 postpartum while 20 cows of G2 presented mucopurulent discharge which disappeared lately in day 37. In contrast, G3 have purulent discharge which needed a longer time (52 day postpartum) to disappear. Therefore, it is concluded that retained placenta can be treated effectively by chlortetracycline which also provide a good prevention against incidence of puerperal metritis.

**Keywords** | Chlortetracycline, Dairy cows, Local intrauterine route, Oxytetracycline, Retained placenta.

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## INTRODUCTION

Retention of the Fetal Membranes (RFM) means the failure of the fetal membranes to detach and to expel from the uterus during the physiological third stage of parturition. Retention has two types which includes primary and secondary. The primary retention occurs when the fetal

membranes failed to detach from the maternal caruncles. The secondary one resulted from mechanical difficulty of expulsion due to uterine atony while the membranes are already detached (Eiler and Fecteau, 2007, Patel and Parmar, 2016).

The RFM delayed uterine involution following postpar-

tum anoestrus as well as long open days and calving intervals leading to adversely effected reproductive performance (Abdelhameed et al., 2009). Therefore, cows with RFM presented a prolonged calving interval from the first service and conception. Furthermore, RFM causes a decrease in milk production for 4 weeks after birth and increased risk of endometritis, metritis and mastitis leading to decreased fertility and potential losses in milk production (Beagley et al., 2010).

The current study assumed that usage of local intrauterine antibiotics for treatment of fetal membrane retention led to shorter time of recovery, a reduced incidence of metritis, and would require fewer antibiotics with normal milk production. This study aimed to compare the effect of treatment through local intrauterine application of chlortetracycline and oxytetracycline in cows suffered from retained placenta and its ability to prevent the incidence of puerperal metritis, along with the evaluation of milk yield.

## MATERIALS AND METHODS

### ANIMALS

All procedures were performed according to the guide approved by the Ethics Committee of the Faculty of Veterinary Medicine, Aswan University, Egypt. Total number of 65 pluriparous cows of Holstein Friesian breed was used in current study. They were belonged to a private farm in Qena province of Egypt. The study was performed during the winter (January and February). Experimental cows were milked twice daily (at 6 a.m. and 6 p.m.) with a milking machine and fed on total mixed ration (TMR). The average daily milk production of the cows was 15 kg.

### CLINICAL EXAMINATION

Experimental cows were examined daily for the presence of any disease and detection of rectal temperature was done for further confirmation. All cows were examined after calving for detection of bleeding and any periparturient disease conditions. The examination procedures included detection of the body condition score; furthermore, intravaginal examination and transrectal palpation were also performed. Cases failed to expel the placenta within 12-24 hours or more after calving were defined as RFM cows (Fourichon et al., 2000) and were submitted for treatment protocols.

### TREATMENT

Cows were divided into three treatment groups: Group one, (G1, n=25) which received 5 g chlortetracycline (chlortetracycline oblets – Phenix, chlortetracycline hydrochloride 1000 mg ) locally by intrauterine route daily for three days (total 15 g). Group two (G2, n=25) which received 5 g oxytetracycline Hcl (Oxyvet-pharma; Pharma Swede, Egypt),

in the form of tablets (oxytetracycline 500 mg/tablet), by intrauterine route once daily for three days. Group three (G3, n=15) received no treatment known as control group. If any experimental cases presented fever, they would receive systemic treatment with 10 mg/kg of body weight of amoxicillin for three to five consecutive days.

Each cows was considered clinically cured after complete shedding of the placenta within the first three days of treatment (Cui et al., 2014). Regarding to the occurrence of puerperal metritis as a complication of fetal membrane retention, the proportion of cows that could avoid puerperal metritis was detected within the 21 days of parturition.

### ULTRASONOGRAPHY AND RECTAL PALPATION

After treatment of RFM, examination of the cervix, uterine body and horns by rectal palpation and transrectal ultrasonography was carried out three times a week until 60 days of parturition.

Detection of the location and consistency of the inner genitals was done by rectal palpation, while examination of uterine involution was performed by transrectal palpation and confirmed by transrectal ultrasonography. The location of the uterus was assessed as being either clearly in the abdomen or in or almost inside the pelvic cavity. For ultrasonography, a real-time B-mode linear array scanner (Aloca SSD-210 DXII, Aloca Corp. Ltd., Tokyo, Japan) with a 5 mhz transducer was used. For detection of the degree of involution, the following steps were done. First, the cervix was examined by detection of its caudal end and measurement of the area immediately in front of this end. Second, after the bifurcation, the two uterine horns were checked and examined for the diameter, uterine contents and endometrial appearance. The results from checking the cervix and the uterus were evaluated by comparing each observation with a basal line. Detection of the baseline depended on the average of the recordings from the last two weeks of the experiment (after completion of the involution). Involution is considered to occur when the diameter of the cervix and the uterine horn do not excess the basal level by 20% (Königsson et al., 2001).

After the treatment of RFM, the cows were examined for the presence of puerperal metritis. The cows were considered to have puerperal metritis, if the uterus was flaccid and nonretractable with red-brown watery vaginal discharge while detection of temperature revealed it was more than 39.5 °C during 21 days of postpartum (Sheldon et al., 2009). Scoring of vaginal discharge included one for clear, two for mucopurulent and three for purulent (Königsson et al., 2001; Williams et al., 2005; Braga Paiano et al., 2019).

Feeding and daily energy intake of each cow was recorded.

**Table 1:** Comparison of the time of placental shedding, number of Holstein Friesian cows developed puerperal metritis and numbers of cows suffered from fever in groups of chlortetracycline, oxytetracycline and non-treated control group.

Groups	Time of complete expulsion of placenta (days)	Number of cows success to expel placenta	Number of cows developed puerperal metritis	Time of development of puerperal metritis (days)	Number of cows suffered from fever within first 10 days
Chlortetracycline G1 (n= 25)	3	21	0	0	0
Oxytetracycline G2 (n=25)	5	15	0	0	5
Control G3 (n= 15)	8	5	12	3	10

**Table 2:** Description of the uterine involution in Holstein Friesian cows with retained placenta after treatment with chlortetracycline, oxytetracycline and non-treated cows

Groups	Median time of uterus to be in pelvic cavity (days)	Median time of cervical involution (days)	Median time for pregnant uterine horn involution (days)
Chlortetracycline G1 (n= 25)	21 <sup>a</sup>	30 <sup>a</sup>	21 <sup>a</sup>
Oxytetracycline G2 (n=25)	30 <sup>b</sup>	37 <sup>b</sup>	30 <sup>b</sup>
Control G3 (n= 15)	45 <sup>c</sup>	45 <sup>c</sup>	37 <sup>c</sup>

Results are shown as median (range). Values bearing different superscripts in the same column differ significantly (P<0.05).

All of the offered food was checked daily and the uneaten food was weighed and recorded. Appetite rate was used as a method for evaluating how much the animal suffered from the disease (general appearance) (Königsson et al., 2001). Lacking in appetite meant the cow failed to eat all the offered food. During the first 50 days after parturition, mean daily energy intake (MJ/day) at different intervals was recorded and used as a method for assessment of food intake (Königsson et al., 2001). Progress of food consumption was detected by comparing the daily energy intake with the highest recorded daily intake during the experiment (Königsson et al., 2001). The day on which the animal reached 90% of the maximum intake was recorded. Body weight and milk production were also recorded daily.

**STATISTICAL ANALYSIS**

The mean parameters of the different groups were compared and differences among means were detected by using one-way analysis of variance. Tukey’s test (SPSS 20, IL, USA) and was used to detect significant differences among means. P < 0.05 was considered for statistically significant difference.

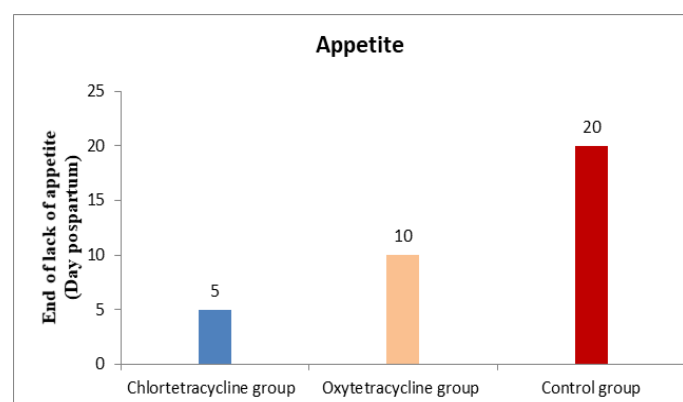
**RESULTS**

In G1, 21 cows out of 25 cows had complete shedding of the placenta within the first three days of treatment, whereas in G2, 15 out of 25 cows had the complete shedding within five days of the treatment. On contrary, G3 (control group) failed to expel the placenta completely within the same period and only 5 cows expel the placenta within 8 days (Table 1).

In the current study, G1 with intrauterine application of antibiotics didn’t present any case with fever. In G2, 20% of the cows (5 cows) suffered from fever while the ratio increased in G3 to be 66.7% (10 cows) due to absence of antibiotic treatment. None of the cows developed puerperal metritis in G1 and G2, but 80 % (12 cows) of control group suffered from puerperal metritis after three days of calving (Table 1).

**CLINICAL EXAMINATION AND GENERAL HEALTH**

Results from recordings of food intake and milk production are demonstrated in figures 1-4. The cows in G1 had shorter periods of reduced appetite around parturition (five days from parturition) while the period of lack of appetite in G2 and G3 extended to 10 and 20 days after parturition, respectively (Figure 1).

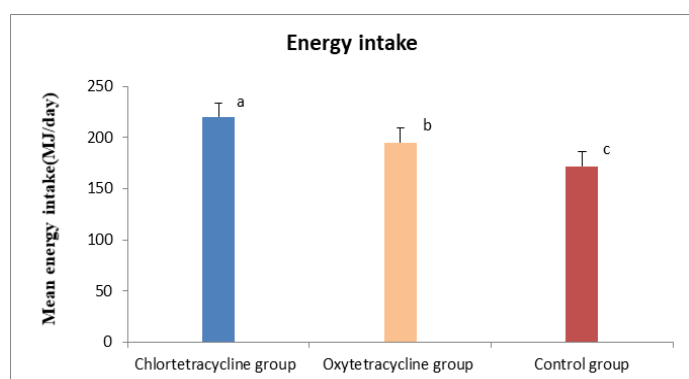


**Figure 1:** End of lack of appetite (day postpartum) in Holstein Friesian cows with retained placenta after treatment with chlortetracycline, oxytetracycline and non-treated control cows.

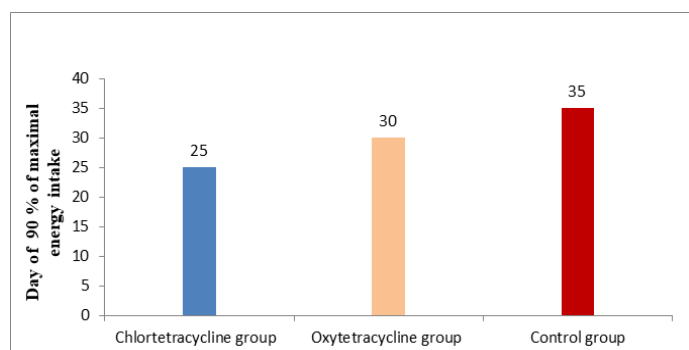
**Table 3:** Description of the vaginal discharge in Holstein Friesian cows with retained placenta after treatment with chlortetracycline, oxytetracycline and non-treated cows

Groups	Number of cows has purulent vaginal discharge > 26 day	Number of cows has mucopurulent vaginal discharge > 26 day	End of mucopurulent vaginal discharge (day p.p.)
Chlortetracycline G1 (n= 25)	1	15	32
Oxytetracycline G2 (n=25)	5	20	37
Control G3 (n= 15)	15	10	52

There was a significant difference between the groups in energy intake. The energy intake in G1 was significantly higher ( $p < 0.05$ ) among the groups as it was 220 MJ/day and had reached to this level in day 25 of calving. While in G2, it was 195 MJ/day after one month of parturition. In G3, it was 172 MJ/day and this had been achieved in day 35 of parturition (Figure 2 and 3).



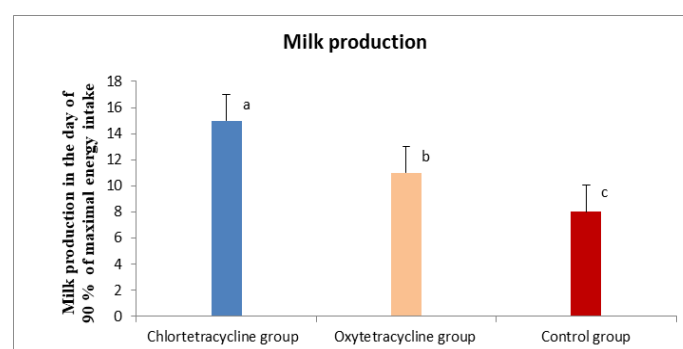
**Figure 2:** Mean energy intake (MJ/day) in Holstein Friesian cows with retained placenta after treatment with chlortetracycline, oxytetracycline and non-treated control cows. Results were presented as Mean±standard error. Values with different letters (a, b and c) differ significantly ( $P < 0.05$ ).



**Figure 3:** Day of 90% of maximal energy intake in Holstein Friesian cows with retained placenta after treatment with chlortetracycline, oxytetracycline and non-treated control cows.

There was a significant difference between the groups in milk production. The milk production in G1 was significantly higher ( $p < 0.05$ ) than G2 and G3 and reached to 15 liter in G1. In G2 the milk production presented significant decrease ( $p < 0.05$ ) to be 11 L whereas the considerable decrease was in G3 as it became 8 L (Figure 4).

Figure 4: Milk production in the day of 90% of maximal energy intake (Liter) in Holstein Friesian cows with retained placenta after treatment with Chlortetracycline, oxytetracycline and non-treated control cows. Results were presented as Mean ± standard error. Values with different letters (a, b and c) differ significantly ( $P < 0.05$ ).



**Figure 4:** Milk production in the day of 90% of maximal energy intake (Liter) in Holstein Friesian cows with retained placenta after treatment with Chlortetracycline, oxytetracycline and non-treated control cows. Results were presented as Mean ± standard error. Values with different letters (a, b and c) differ significantly ( $P < 0.05$ ).

**ULTRASONOGRAPHY AND RECTAL PALPATION**

Results from ultrasonographic examinations have been indicated in Table 2. Examination presented the required duration for the involution of the pregnant uterine horn, for involution of the cervix and demand for the presence of the uterus in the pelvic cavity revealed a significant difference in G1 compared to G2 and G3. The shortest time was used by G1 for involution of the pregnant uterine horn and cervical involution, while G2 required more time for involution of the uterus and cervix. G3 needed the longest period for involution of the reproductive tract.

Results from the vaginal discharge examination have been presented in Table 3. Vaginal discharge examination represented that 15 cows of the chlortetracycline group had mucopurulent discharge which disappeared rapidly in day 32 postpartum and only one cow had purulent discharge. From oxytetracycline group, 20 cows presented mucopurulent discharge which disappeared lately in day 37 postpartum and five cows had purulent discharge. In contrast, most of the cows in the control group had purulent dis-

charge while only ten cows had mucopurulent discharge which needed longer period of time to disappear in day 52 postpartum.

## DISCUSSION

Trials based on finding appropriate treatments for RFM are the most discussed studies either in the literature or among practitioners. The principal purposes of treatment are the expulsion of toxic and inflammatory products from the uterus, control of systemic shock symptoms, endotoxemia, and prevention of laminitis (Canisso et al., 2013). Oxytocin, antibiotics, and uterine lavage are considered the most essential treatments (Perkins, 1999).

In the present study, the chlortetracycline treatment caused a significantly higher ( $p < 0.05$ ) reduction in the time of recovery from the retained placenta compared to the oxytetracycline group and control group. Chlortetracycline is a bacteriostatic antibiotic with no post-antibiotic effects. Thus, the intrauterine administration of chlortetracycline was clinically effective for the management of a retained placenta. This favorable efficacy of chlortetracycline is from two aspects which are its ratio of distribution and bioavailability.

The pharmacokinetic parameter described drug distribution as an estimator of drug diffusion to tissues which was known as the apparent Volume of Distribution (Vd).

Chlortetracycline has a greater Vd in comparison with oxytetracycline, which indicated chlortetracycline can distribute extensively in tissues (Del Castillo et al., 1998).

Regarding drug bioavailability which indicates the rate and extent of drug absorption, both antibiotics chlortetracycline and oxytetracycline were much different in their levels of absorption. Bioavailability of chlortetracycline was three-fold greater than oxytetracycline (Del Castillo et al., 1998).

In spite of oxytetracycline was recommended by veterinarians for treatment of retained placenta, this therapy has not proved its ability for earlier release of retained fetal membranes and present study has confirmed it, too. This result coincided with a previous study carried out by Königsson et al. (2001) who reported that in animal group treated with antibiotic (oxytetracycline) the placenta was still attached and they shed their placenta later than those did not treat with antibiotic.

In the current study, based on results from G1 treatment group, it was obvious that local intrauterine application of antibiotics as a treatment method of RFM was effective

in preventing the incidence of fever. The potency of the antibiotic plays important role in incidence of the fever, thus in G2, 20% of the cows suffered from fever while the incidence of fever had increased in G3 to 66.7% due to no antibiotic treatment was received.

These results were in accordance with a previous study indicated that the proportion of cows with fever was higher in control group with manual removal of the retained placenta as a method of treatment, in comparison to the other two groups in which local intrauterine application of antibiotics was applied as a method of treatment (Drillich et al., 2006).

The RFM occurred in the early postpartum period in cows (Beagley et al., 2010). Retention of the fetal membrane threaten animal life due to the development of puerperal metritis (Han and Kim, 2005). Puerperal metritis was known as the main cause of reduced fertility in animals with retained placenta. Therefore, perfect medical treatment for RFM should prevent the occurrence of puerperal metritis. The most common treatment of retained placenta in cows is local or systemic antibiotic.

In the current study, both chlortetracycline treatment and oxytetracycline succeeded in prevention the occurrence of puerperal metritis, while the control group failed to do it. In control group, eight cows (53%) suffered from puerperal metritis within 3 days of calving.

This result was in correspond with Drillich et al. (2005) who found that antibiotic treatment of retained placenta by a local route through intrauterine application resulted in a low incidence of acute metritis than the control group which had no treatment. However, recent reports indicated that usage of antibiotic either locally inside the uterus or systemically had low efficacy in hastening the detachment and expulsion of the retained placenta (Drillich et al., 2006, Drillich et al., 2007, Haimerl and Heuwieser, 2014). Thus, the challenge was to find an antibiotic with good efficacy to hasten the separation and detachment of the retained placenta and also without any side effect in milk production or composition.

Protein-binding was important because only free tetracycline molecules were able to cross through the blood vessels and move into the tissues. Protein binding significantly impacts clinical efficacy only when the degree of binding exceeds 85% to 90%, and both chlortetracycline and oxytetracycline had fewer protein binding levels than their threshold (Del Castillo et al., 1998). This might explain how both antibiotic groups had protection against the incidence of puerperal metritis.

In the current study, the cows in G1 had shorter period of reduced appetite around parturition, while the period of loss of appetite in G2 was slightly increased. On the contrary, G3 which received no treatment has the longest period of lack of appetite which lasted for 20 days. At the same time, the energy intake in G1 was significantly higher ( $p < 0.05$ ) among the groups and reached to this level of highest energy intake earlier than other groups. While in G2, it was lower than G1 and needed more time to reach this level. In G3, the energy intake was the lowest and took more time than G1 and G2.

These results were in agreement with Königsson et al. (2001) who revealed that the groups of cows received early treatment with antibiotic began to eat earlier and subsequently had higher daily energy intake compared to other retained placenta cows. Therefore, the lack of appetite ended, which was the most important factor for the negative energy balance.

In the current study based on 305 days (the standard period of milk production) of milk yield, the control group produced less milk than other groups. This indicated that retention of the placenta leads to a drop in milk production. Previous studies failed to present a close relationship between retention of the placenta and decreased milk yield due to failure to notice the short term fluctuations in milk production caused by the retention of the fetal membranes (Königsson et al., 2001, Fourichon et al., 1999).

In the current study, milk production in G1 did not affect by the chlortetracycline treatment, whereas, in G2, treatment with oxytetracycline led to a slight decrease in milk yield. These results were in the same line with the previous study (Patel and Parmar, 2016) which indicated that milk yield was suppressed for about 4 weeks after calving with retained placenta. The RFM had been associated with increased risk for endometritis, metritis and mastitis, which can lead to decreased fertility and potential losses in milk production (Beagley et al., 2010). Sheldon et al. (2004) also reported that retained placenta was associated with a substantial reduction in milk yield that persisted even after solving the problem so that the affected animals during the first 2 months of lactation produced 355 L less than normal cows.

In the current study, there was a significant difference ( $p < 0.05$ ) between all groups in the time required for the involution of the pregnant uterine horn, involution of the cervix and the period required for the presence of the uterus in the pelvic cavity. The shortest time was used by G1 for involution of the pregnant uterine horn and cervical involution, while G2 required more time for involution of the uterus and cervix. G3 needed the longest period of time for

involution of the reproductive tract.

These results converged with Abdelhameed et al. (2009) who reported that RFM delayed uterine involution leading to postpartum anoestrus as well as long open days and calving intervals. Furthermore, RFM was usually accompanied by an adversely reproductive performance. Cows with reproductive disorders had longer intervals from calving to the first service and conception, thus they required more service per conception that led to lower pregnancy rate. The results of the current study did not concur with Königsson et al. (2001) who found that the using either oxytetracycline or flunixin or even combination of them in treatment of retained placenta resulted in no obvious differences between these different treatment protocols. Furthermore, in the same study involution of the pregnant uterine horn, the cervical involution and the time for the first finding of the uterus in the pelvic cavity were similar in all groups.

Examination of the vaginal discharge at the end of the postpartum period to detect its characteristics either mucopurulent or purulent was regarded as a sign for chronic inflammation of the genital tract. However, in-field applications or dairy farms, the vaginal inspection was not a standard procedure. In the current study, chlortetracycline succeeded in prevention of severe chronic infection except in one cow that suffered from purulent vaginal discharge. The most cows of the chlortetracycline group presented mucopurulent vaginal discharge which ended early in day 32 postpartum. In G2, five cows revealed purulent discharge while 20 cows revealed mucopurulent discharge that ended later in day 37 postpartum. On the contrast, most of the cows in the control group had purulent discharge and a small portion presented mucopurulent discharge which needed a longer time to end in day 52 postpartum. Thus, these results revealed that an intrauterine treatment of chlortetracycline has a positive effect on preventing the occurrence of chronic inflammation of the genital tract. These results did not harmonize with Drillich et al. (2007) who reported no significant difference in vaginal discharge between the group of cows suffered from the retained placenta and treated with antibiotics by the local intrauterine route and the other groups which treated with a systemic route.

## CONCLUSION

This study concluded that local intrauterine application of chlortetracycline is clinically effective for the management of a retained placenta, including higher clinical cure rates, shorter time for recovery, normal milk production and a tendency to prevent the occurrence of puerperal metritis. The mechanism of the action of chlortetracycline on pla-

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

Dr.Yahia and Dr.Asem designed the current research, while Dr.Yahia performed analysis or interpretation of data. Dr.Yahia wrote the original draft. Dr.Yahia and Dr.Al Shaimaan revised the draft of the manuscript. All authors reviewed the manuscript and approved the submitted version.

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