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# The Effect of CIDR Treatment in Estrus Synchronization on Insulin Like Growth Factor in Iraqi Ewes

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***Authors' contributions***

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## ABSTRACT

The aim of study the ability of CIDR alone and in combination with PMSG in improving the fertility potential of the ewes and Determine the concentration of insulin like growth factors in blood of studied animals. Eighteen multiparous local Iraqi ewes aged between 3-4 years were randomly divided into three groups (n= 6/ group). Ewes were synchronized by CIDR The total number of animals used in the experiment was Eighteen ewes, The animals were subdivided into three groups; Group1 (n=6) ewes treated with CIDR for 12 day and treated with a single dose of intramuscular injection of PMSG 500 IU at the time of CIDR removal. Group 2 (n=6) non pregnant ewes treated only by CIDR, which applied by intra-vaginal route for (12 days), then withdrawal. Group3 (n= 6) ewes control without treatment throughout the study. Regarding the insulin like growth factor (IGF-I), a significant upward increase in the level of the mentioned factor was observed as the study periods progressed in the treatment groups compared to the control group,

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which maintained similar levels of the studied factor in the different study periods. The period at lambing also recorded the highest level of the hormone under study, at a level of 21.61 ng/ml. A gradual significant ($p<0.05$) increase was also observed with the progression of the study and pregnancy periods in the level of insulin like growth factor-1 in pregnant studied animals compared to those that did not become pregnant, which maintained close and almost constant levels despite the progression of the study periods. The period at the end of pregnancy and near birth (at lambing) also recorded the highest levels of the aforementioned factor at a level of 24.21 ng/ml. The results of the current study recorded a significant superiority ($p<0.05$) in the weights of single births, males and females, compared to twins that gave births with lower weights, with significant superiority($p<0.05$) for single male births compared to those of single females. The treatment groups in the current study recorded a clear significant superiority ($p<0.01$) in the pregnancy rate compared to the control group in which the pregnancy rate was 0%, in addition to the large difference, but not significant between the treatment groups themselves, as group G1 gave a much higher percentage compared to group G2, at 83% and 33% for the two treatment groups, respectively. The treatment groups showed a clear significant superiority in the lambing rate compared to the control group, in which the birth rate was 0%. The difference was also noted between the treatment groups themselves, as the G1 group recorded a lambing rate of 100%, which is higher than the lambing rate given by the G2 group, which did not exceed 33%.

*Keywords: CIDR; PMSG; Ewes; pregnancy; Iraq.*

## 1. INTRODUCTION

Ewes are animals that exhibit seasonal polyestrous behavior. The breeding season is characterized by regular intervals of 16-17 days of estrus behavior and ovulation (Hussain et al., 2017, Hatif and Younis, 2018). Also Younis et al. (2019). However, during the mid-anestrus period, there is a cessation of cyclic ovulatory activity (Dehkordi et al., 2022). These animals are influenced by seasonal fluctuations in environmental conditions, with changes in day length playing a crucial role in controlling the breeding season (Hatif and Younis 2018a and b). Reproductive activity occurs during shorter days, while it diminishes during winter and spring as the day length increases (Al-Mutar, 2017 and Younis et al., 2020). The length of the breeding season varies between two to three estrus cycles (Taher, 2014) and in certain tropical breeds, cyclic activity occurs throughout the year, with ewes going into estrus approximately 21 times a year due to the effect of latitudes (Abdul Hussain et al., 2017). In sheep, the experimental modification of photoperiod, without a change in other factors can shift the timing of the breeding season. The reversal of the annual photoperiodic cycle causes the reproductive season to shift by six months (Younis et al., 2020). In addition, within six months, ewes exposed to light regimes that provided a natural annual variation in day length, have two breeding seasons per year. during the Spring photoperiod. that nocturnal melatonin concentration is higher than diurnal concentrations in seasonal and non- seasonal local Awassi ewes at spring (Hatif and Younis, 2018). It is clear that short days are stimulatory and long days are inhibitory at short time (Forcada and Abecia, 2006). Modifications to the activity of the hypothalamic-pituitary axis through changes in pulsatile gonadotrophin releasing hormone (GnRH) and luteinizing hormone (LH) control the seasonal changes in ovine reproductive condition. Such modifications reflect differences in sensitivity to the negative feedback of circulating oestradiol (Smith et al., 2010). Estrous synchronization is manipulation of the bovine estrous cycle to result in the majority of animals exhibiting standing estrus in a short period of time (Tamer and Al-Hamedawi, 2013). It is a very effective method to increase the proportion of animals that are bred at the beginning of the breeding season (Larson and Randle, 2008). One of the advanced managemental processes through which the humane errors and managemental costs could be minimized is synchronization of estrus (Al-Hamedawi, et al., 2016, Al-Hamedawi, et al., 2020). It is The primary benefits of utilizing a synchronization protocol containing P4 are its ability to induce estrus out of breeding season, along with its high pregnancy rates and litter size. Yu et al., 2022 reported that the conception rate was 74-80% and the twining rate was 55-70% after cervical or intrauterine fixed-time artificial insemination. The P4 regimens mainly composed of P4 treatment for different days with equine Chorionic Gonadotropin (eCG) and/or Prostaglandin F2alpha (PGF2α) ( Kadhim and Hussain, 2014). (Kadhim and Hussain, 2024a).

Inserting of an intravaginal 0.3 g P4-containing device caused elevation in serum P4, which blocks follicular dominance and stimulates follicular turnover that allows a new follicular wave to emerge within 3 or 4 days (when P4 level fall) in goats and sheep (Vilariño et al., 2013).

Insulin-like growth factor 1 (IGF 1), also known as somatomedin C, is a protein that is encoded by IGF-1 gene . (Höppener et al., 1985) . IGF 1 is a protein that cells use to communicate with each other and with their surroundings. IGF 1 is part of a complex system that includes two cell surface receptors (IGF 1R and IGF 2R), two ligands (IGF 1 and IGF 2), six IGF binding proteins (IGFBP 1–6), and IGFBP degrading proteases. IGF 1 is an important component of the somatotropic axis, which also includes growth hormone (GH) and its receptors. The liver produces the majority of the circulatory IGF 1 in response to GH. It has a negative feedback effect on the pituitary gland, regulating GH secretion. The role of IGF-1 has been conserved throughout species evolution, and the increasing of its activity has been linked to fertile reproductive patterns. It is essential for nutrient utilization and metabolism in ruminants and lactation and energy balance have governed them (Rhoads et al., 2008). It has been reported that plasma IGF1 concentrations differ between breeds (Roberts et al., 1990). Insulin-like growth factor-1 IGF-1 is implicated in follicle development and is considered to mediate the actions of growth hormone GH and gonadotrophins at the ovarian level. However, the expression and secretion of IGF-1 by the ovary are controversial, partly because of species and cell-type specificity. The present study investigated whether IGF-1 is produced by ovine granulosa cells and whether its production is regulated by GH and follicle stimulating hormone FSH. (Khalid et al., 2000). IGF 1 gene is found on chromosome 5 in ovine and is also found in other species. IGF 1 is known to act in all three ways, namely endocrine, paracrine, and autocrine (Butler et al., 2002). (Sun et al., 2011). discovered that brain IGF 1 receptors and estrogen receptors interact to regulate female reproduction and behavior. IGF 1 stimulates estrogen sensitive neurons via IGF1 receptors, thereby mediating estrogen stimulation of GnRH neurons and, as a result, GnRH release (Wolfe et al., 2014). Female reproductive life can be divided into several stages, including puberty, the period of recurring estrous cycles, pregnancy, and the postpartum period. IGF 1 is linked to all of these different stages of female reproduction. Age at puberty is a major determinant of ruminant reproductive efficiency over a lifetime. Season, age, nutrition, and body weight of animals are factors influence puberty age (Schillo et al., 1992). The decrease in plasma IGF1 concentration delayed puberty due to a delay in follicle growth, decrease in estradiol content, and possibly delays in LH surge (Velazquez et al., 2008). The luteal and follicular phases of the cattle estrous cycle are involved. Gonadotropin secretion in the ovary influences gametogenesis, foliculogenesis, ovulation, corpus luteum function and steroidogenesis during these two phases. The secretion of gonadotropins is controlled by a delicate balance of hormonal interactions in the hypothalamic-pituitaryovarian axis, which in turn controls the development and regression of ovarian follicles and the corpus luteum . IGFs may play a role in the selection of follicles for development, according to (Beg and Ginther, 2006). IGF 1 supplementation to culture medium increased granulosa cell proliferation and estradiol production, according to in vitro studies (Mani et al., 2010). Theca cells have been shown to regulate granulosa cell activity and increase testosterone secretion (Spicer et al., 2002). Intrafollicular IGF 1 stimulates oocyte and follicular differentiation via an autocrine and paracrine pathway (Silva et al., 2009). discovered a higher concentration of IGF 1 in the blood of twinned ewes, implying that the IGF system may prime the dominant follicle more towards LH than FSH ( Al-Zubaidi ). For a successful pregnancy, the embryo must be implanted in the uterus after conception and develop normally into a viable fetus. Because IGF 1 receptors are present on the uterus. (Richterich et al., 2007). found that adding insulin and IGF1 to in vitro cultures of bovine embryos had a positive effect on embryo development and favored the development of bovine embryos to the morula stage. (Block, 2007). IGF 1 is also luteotropic in action, stimulating progesterone production from the maternal corpus luteum. Appropriate maternal progesterone plasma concentrations, in turn, stimulate the production of Interferon –tau by ovine embryos for successful pregnancy recognition . (Martal et al., 1997). discovered a higher concentration of IGF 1 in pregnant ewe plasma compared to nonpregnant ewe plasma (Stremming et al., 2021). Maternal plasma IGF 1 concentration influences the energy balance, average daily gain, and nutritional regulation of postpartum reproductive performance in ewe . Less IGF-1 in the circulation of postpartum crossbred heifers has resulted in anestrus (Funston, 1993).

According to (Strauch, 2002). circulating plasma IGF 1 concentration is negatively correlated with the postpartum interval to first ovulation. This could be due to the positive effect of plasma IGF 1 on estradiol secretion by the dominant follicle, which stimulates LH secretion by the anterior pituitary (Velazquez et al., 2008). On the other hand, it has been discovered that a decrease in plasma IGF 1 concentration and gene expression in the early postpartum period may have an effect on reproductive organs and early embryo development. To control the decline in fertility, the body must regain energy balance and optimal concentrations of metabolic hormones such as IGF1 (Llewellyn et al., 2007).

## 2. MATERIALS AND METHODS

### 2.1 Experimental Animals and Management

Eighteen multiparous local Iraqi ewes with an average age between 3-4 years were studied. All animals were housed in one flock. Two breeding rams were used for heat detection and breeding. The experiment was conducted at Veterinary College/ Baghdad University. The experiment span extended from February to October 2023. The ewes were housed in medium management conditions and during the study period alfalfa and hay straw Dry fodder were given. All experimental ewes were checked by transrectal ultrasonography and transabdominal ultrasonography (Chison ECO2/China), and it was confirmed that they were empty. Preventive health measures will applied such as vaccination against enterotoxaemia and treatment against internal &external parasite.

### 2.2 Experimental Design

#### 2.2.1 The animals were subdivided into three groups

Group1 (n= 6) ewes treated with CIDR for 12 day, and treated with a single dose of intramuscular injection of PMSG 500 IU at the time of CIDR removal. Group 2 (n=6) non pregnant ewes treated only by CIDR, which applied by intra-vaginal route for (12 days), then withdrawal. Group3 (n= 6) ewes control without treatment throughout the study; Animals were monitored on a daily basis, and the time of estrus and mating was recorded. Pregnancy was monitored, as well as the time of delivery. The gender of the offspring, the number of embryos and the status of the embryos were also recorded.

#### 2.2.2 Estrus synchronization protocol, estrus detection, and breeding

The total number of animals used in the experiment was eighteen ewes, twelve non-pregnant ewes were taken from them and the CIDR was synchronized and divided equally into two groups. It was inserted through the vaginal root by a special tool. It was maintained for 12 days and then withdrawn. At the time of CIDR removal, eCG (500 IU) was given to one group.

#### 2.2.3 Estrus detection and mating after synchronization

The heat was detected by observing the mating of the breeding ram, and also by examining the external and internal genital organ's softness and the presence of mucus. During the estrus period, sexual activity was checked every half hr, from 08:00 am to 01:00 pm, and day 0 was considered a day of breeding. Each ewe was considered in estrus when observed to accept a service from a ram, the day of breeding was considered day 0.

#### 2.2.4 Blood collection for hormonal assay.

The blood collected 10 ml from the jugular vein by vacuum gel tubes. On days 0, 12, 60 and at lambing to determine Insulin like growth factors. Serum was collected after centrifugation with 3000 RPM for 10 minutes. Serum was kept in epindroff tube at -18ºC until analysis of hormonal concentrations by Abbott TECTplus immunoassay analyzer (Socheh et al., 2019).

## 3. RESULTS AND DISCUSSION

Regarding the insulin like growth factor (IGF-I), a significant upward increase in the level of the mentioned factor was observed as the study periods progressed in the treatment groups compared to the control group, which maintained similar levels of the studied factor in the different study periods. The period at lambingalso recorded the highest level of the hormone under study, at a level of 21.61 ng/ml (Table 1).

IGF-I is synthesized by corpora lutea and ovine granulosa cells (Perks et al., 1995). When measuring plasma IGF-I concentrations over the course of two consecutive estrous cycles in

**Table 1. Changes in insulin like growth factor (IGF-I) concentration in estrus synchronized ewes during CIDR treatment (ng/ ml)**

| | Mean ±SEM | | | |
|---|---|---|---|---|
| **Groups** | **Day 0** | **At day 12 of treatment** | **60 Days** | **At Lambing** |
| G1 | 1.537 ±0.18 Ad | 6.35 ±0.63 Ac | 9.46 ±1.72 Ab | 21.61 ±4.55 Aa |
| G2 | 1.208 ±0.15 Ac | 6.09 ±0.68 A ab | 4.21 ±1.54 Bb | 7.67 ±4.06 Ba |
| Control | 1.457 ±0.12 Aa | 1.250 ±0.13 Ba | 1.403 ±0.16 Ca | 1.310 ±0.14 Ca |

*LSD value= 2.182*; Means with different big letters in the same column and small letters in the same row are significantly different. *(P≤0.05)*

sheep (Leeuwenberg et al., 1996) found an increase around the second pre ovulatory LH surge, but failed to find an increase around the first LH surge. IGF-I concentrations in follicular fluid have been suggested to increase with follicle growth in cattle (Spicer and Echternkamp, 1995). During ewes' estrus, IGF-I mRNA concentrations reach their peak in the oviduct wall's muscle and mucosa layers (Wathes et al., 1998). In the endometrium and myometrium of the ovine uterus, IGF-I mRNA concentrations increase during estrus (Stevenson et al., 1994). These results suggested that variations in plasma IGF-I concentrations seen during the ewe's estrous cycle could be caused by locally generated IGF-I.(Uniyal et al., 2015). There is a substantial correlation between plasma IGF1 and P4 concentrations (Langendijk et al., 2008). Throughout the estrous cycle, sheep's plasma IGF1 concentration varies. This scientific fact explained the progressive increase in the level of this factor recorded by our study as the study period progresses and pregnancy progresses as a result of the increasing need for the progesterone hormone for which this factor is responsible, which causes its level to rise as the pregnancy period progresses, reaching its peak at the end of pregnancy and coinciding with lambing time. On the other hand, IGF concentrations in follicular fluid are negatively correlated with the estrogenic condition of the follicles (Funston et al., 1996). As follicles matured, oestradiol concentrations in follicular fluid rose significantly whereas intra-follicular IGF concentrations fell As follicles matured, oestradiol concentrations in follicular fluid rose significantly whereas intra-follicular IGF concentrations fell. Therefore, compared to non-ovulatory follicles, IGF concentrations in potential ovulatory (oestrogenic) follicles were considerably lower (Khan, 2014). Another study conducted in this scientific branch revealed a significant negative correlation between IGF concentrations and follicles' oestrogenic status; however, when follicle diameter was the only factor considered, no such correlation was found between IGF concentrations in follicular fluid and follicular development (Khalid and Haresign, 1996). A gradual significant (p<0.05) increase was also observed with the progression of the study and pregnancy periods in the level of insulin like growth factor-1 in pregnant studied animals compared to those that did not become pregnant, which maintained close and almost constant levels despite the progression of the study periods. The period at the end of pregnancy and near birth (at lambing) also recorded the highest levels of the aforementioned factor at a level of 24.21 ng/ml (Table 2).

Female reproductive life can be divided into several stages, including puberty, the period of recurring estrous cycles, pregnancy, and the postpartum period. IGF is linked to all of these different stages of female reproduction (Schillo et al., 1992). (Sun et al., 2011) discovered that brain IGF receptors and estrogen receptors interact to regulate female reproduction and behavior. IGF stimulates estrogen sensitive neurons via IGF-1 receptors, there by mediating estrogen stimulation of GnRH neurons and, as a result, GnRHrelease (Nuttinck et al., 2004). (Moyes et al., 2003) referred a higher

**Table 2. Changes in insulin like growth factor-1 concentration of pregnant compared with non-pregnant**

| **Groups** | **Day 0** | **At day 12 of treatment** | **60 Days** | **At Lambing** |
|---|---|---|---|---|
| Pregnant | C1.40±0.16 a | BC6.04±0.62 a | B8.33±1.80 a | A24.21±1.95 a |
| Non-pregnant | A1.40±0.10 a | A3.62±0.87 a | A2.92±0.95 b | A1.27±0.07 b |
| LSD | 2.70 | | | |

*Means with different big letters in the same row and small letters in the same column are significantly different* concentration of IGF in pregnant cow plasma compared to non-pregnant cow plasma. (IGF) is a hormone that can regulate growth, especially during early development.(Spagnoli et al., 1996) After parturition, IGF is passively transferred through colostrum, which has a very high concentration and declines dramatically to a very low concentration a few days after birth On the other hand, it has been discovered that a decrease in plasma IGF concentration and gene expression in the early postpartum period may have an effect on reproductive organs and early embryo development (Grosvenor et al., 1993). To control the decline in fertility, the body must regain energy balance and optimal concentrations of metabolic hormones such as IGF, which find out that a significantly increase in pregnant ewes bearing twin embryo/fetuses than in pregnant ewes bearing a single embryo/fetuses in day 30 and 76 of gestation (Igwebuike, 2010). also argued that it can distinguish between single-foetus and multi foetus pregnancy on the 19th day of gestation in cross breed ewes, From all the above mentioned scientific facts, it is clear why the level of IGF-1recorded gradual increased in pregnant ewes in our study by the progression of pregnancy up to lambing time (Younis and Akram, 2023). The results of the current study recorded a significant superiority ($p<0.05$) in the weights of single births, males and females, compared to twins that gave births with lower weights, with significant superiority($p<0.05$) for single male births compared to those of single females (Table 3).

**Table 3. the relationship between the weight and the type of fetus male, female and twin**

| Type of birth | Birth weight |
|---|---|
| Single male | 4.43±0.09b |
| Single female | 4.00±0.10c |
| Twin | 7.20±0.10a |
| LSD | 0.38 |

These results nearly similar to that of (Zarkawi, 2001). in Syrian Awassi ewes who recorded a mean birth weight ranged from (4.5-5.1 kg) by using similar protocol for estrus synchronization and superovulation, Our results also in agreement with the same above researcher in that the single births were heavier than the multiple once. The differences between single and multiple births weights is logical because of highly needing of multiple births to more metabolites that distributed on offspring (Oftedal, 2018). While (Manalu et al., 2000). Ensure that there was no any significant differences between weight of multiple and single births in Javanese thin-tail ewes when they recorded a lamb weights of (1.68 kg) and singles (1.91 kg) respectively. There is also an evidence of superiority in progressing prenatal weights and growth level for the superovulated fetuses in compare to those nonsuperovulated once, which may attributed to increased progesterone levels in superovulated animals comparing to the other, which causing better developing of mammary glands and providing much milk production for offspring (Manalu, Sumaryadi et al. 2000). Another scientific fact its appear that following pregnancy and delivery, sheep with suitable body condition scores are more productive than those in poor condition (Nageye and Koyuncu). The treatment groups in the current study recorded a clear significant superiority ($p<0.01$) in the pregnancy rate compared to the control group in which the pregnancy rate was 0%, in addition to the large difference, but not significant between the treatment groups themselves, as group G1 gave a much higher percentage compared to group G2, at 83% and 33% for the two treatment groups, respectively (Table 4).

**Table 4. Pregnancy rate in ewes in different groups of study**

| Groups | No. | Pregnancy rate % |
|---|---|---|
| G1 | 6 | 83 (5/6) |
| G2 | 6 | 33 (2/6) |
| Control | 6 | 0 |
| P-value | --- | 0.0367 * |

** (P≤0.05)*

Despite a high degree of control of estrus and ovulation, variable reproductive performance and lower conception rates have been observed in ewes bred out-of-season (Husein and Kridli, 2001). Our results were higher than that of (Kuru et al., 2017). In Pirlak ewes which ranged between (37.5% and 48.81%). But its nearly similar the results of (Kuru et al., 2022). In Romanov ewes which were ranged between (72% and 79.2%) and also similar to results of (Eldomany et al., 2023). Who recorded a pregnancy rate of (85.7%) in crossbred ewes breed (Abdel-Khalek et al., 2009). Variation in pregnancy rate with CIDR treatment in different studies might be due to differences in individual ewes body condition, breed and management systems (Yadi et al., 2011). The variation in pregnancy rates were also attributed to type of vaginal devices, kind of progesterone, breed

(Yadi et al., 2011). Individual animal, nutritional conditions (Nosrati et al., 2011). latitude and time of hormonal treatment in the year as suggested by (Ozyurtlu et al., 2010). On the other hand the increased pregnancy rate of ewes in G1 in compare to that in G2 in our study may be due to the positive effect of eCG used in G1 which causing superovulation and increasing the chance of pregnancy and hence increasing pregnancy rate. The treatment groups showed a clear significant superiority in the lambing rate compared to the control group, in which the birth rate was 0%. The difference was also noted between the treatment groups themselves, as the G1 group recorded a lambing rate of 100%, which is higher than the lambing rate given by the G2 group, which did not exceed 33% (Table 5).

**Table 5. Lambing rate in studied ewes in different groups of study**

| Groups | No | Lambing rate % |
|---|---|---|
| G1 | 6 | 117 (7/6) |
| G2 | 6 | 33 (2/6) |
| P-value | 6 | 0 |
| | --- | 0.0296 * |

** (P≤0.05).*

The management of sheep reproduction requires the induction of the ewe estrus cycle and lambing synchronization out-of-season (Gonzalez-Bulnes et al., 2020). Several studies have shown that PMSG application increases the percentage of multiple lambing and prolificacy in sheep as a consequence of an increasing in ovulation rate (Ince and Karaca, 2009). According to (Doğan and Nur, 2006). findings, PMSG stimulates the number of follicles and this caused more follicular development. In our study, lambing rate as in G1 and G2 (100 % and 33 %, respectively). The results of the present study and those obtained by (Belkasmi et al., 2010). are in agreement. The high percentage of lambing rate in our study in compare to other studies may be attributed to the differences in breed used in different studies, differences in progesterone products used in superovulation, different latitude, different seasons in which study conducted, and estrus synchronization programs different latitude, different seasons in which study conducted, and estrus synchronization programs (Yu et al., 2022). It is striking is that the birth rate in most of the studies conducted on sheep in various countries and on different breeds is relatively high, which encourages the widespread application of superovulation and estrus synchronization programs on sheep herds to increase the number of sheep necessary to meet the various human needs for meat, milk, and hides (Redden and Thorne, 2020).

## 4. CONCLUSION

the ability of CIDR alone and in combination with PMSG in improving the fertility potential of the ewes and determine the concentration of insulin like growth factors in blood of studied animals and the treatment groups showed a clear significant superiority in the lambing rate compared to the control group.

## DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have not been used during the writing or editing of this manuscript.

## ETHICAL APPROVAL

Before any experiment performing, the experimental protocol and design used in present study were examined and approved by the Committee of Ethics in College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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