

## ENVIRONMENTAL AND GENETIC FACTORS AFFECTING LITTER SIZE COMPONENTS IN RABBITS

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**Abstract:** In rabbits, ovulation rate is, together with prenatal survival, one of the main limiting factors for litter size. Both components are affected by several factors related to females and their environment. Thus, understanding these components and their factors of variation is key in designing diets, optimisation of reproductive performance and genetic selection. In this review, authors summarise the main components of litter size and their environmental factors of variation. Genetic factors and the main results of genetic selection programmes on components of litter size are also summarised. In this regard, a negative effect of dietary restriction and reduced day light hours is found, as well as a positive effect of body condition, parity order and age of female on ovulation rate. However, an increase in deterioration of oocyte quality has been reported as ovulation rate increases, leading to decreased embryonic and foetal survival. Dietary restriction and heat stress also have a negative effect on embryonic and foetal survival, increasing the failures during gestation while good vascularisation and enough available space in uterine horn are keys to embryonic and foetal survival. Ovulation rate was proposed as indirect selection criterion to improve litter size due to higher heritability. However, this selection was relevant, but it did not modify litter size because of an increase in prenatal mortality. Uterine capacity has been directly related to prenatal survival, although its selection has also been unsuccessful in increasing litter size.

**Key Words:** litter size, ovulation, prenatal survival, rabbits, selection.

## INTRODUCTION

In rabbits, litter size is one of the most important economic traits (Cartuche *et al.*, 2014; Eady and Garreau, 2008). Litter size at birth is related to a sequence of reproductive processes starting from ovulation, fertilisation and prenatal mortality, with the latter component being divided between embryo and foetal mortality (Santacreu *et al.*, 1992). Fertilisation rate is generally high, exceeding 90 to 95% (Peiró *et al.*, 2014), and is therefore not considered a limiting factor for litter size (Belabbas *et al.*, 2016). Therefore, ovulation rate and pre- and post-implantation mortality are the main limiting factors for litter size (Laborda *et al.*, 2011).

There are many environmental and genetic factors that influence the components of litter size and have therefore been extensively studied in rabbits for the purpose of designing diets (see review Martínez-Paredes *et al.*, 2022),

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optimising reproductive management (Theau-Clément *et al.*, 1990) or carrying out genetic programmes (Laborda *et al.*, 2011).

The aim of the present review is to describe some of the main components of litter size and their environmental and genetic factors of variation.

## OVULATION RATE

Rabbit is an induced ovulatory species and ovulation occurs at 11-12 h after mating (Bakker and Baum, 2000; Mattioli *et al.*, 2021). Ovulation rate corresponds to the number of oocytes released during ovulation (Bolet et Bodin, 1992). Ovulation rate is usually estimated as the number of *corpora lutea* in both ovaries, counted in post-mortem after dissection (Bolet *et al.*, 1992) or *in vivo* by laparoscopy (Santacreu *et al.*, 1990). Both measurements have a high regression coefficient (0.9; Santacreu *et al.*, 1990), so laparoscopy is a very accurate technique to measure ovulation rate at day 12 of gestation. Figure 1 shows the follicular structures present in the ovary 72 h and 12 d *post coitum*.

## FACTORS AFFECTING OVULATION RATE

Ovulation rate is influenced by several factors such as body condition, receptivity, parity order, reproductive rhythm and lactation, nutritional status of does, season, photoperiod and genotype.

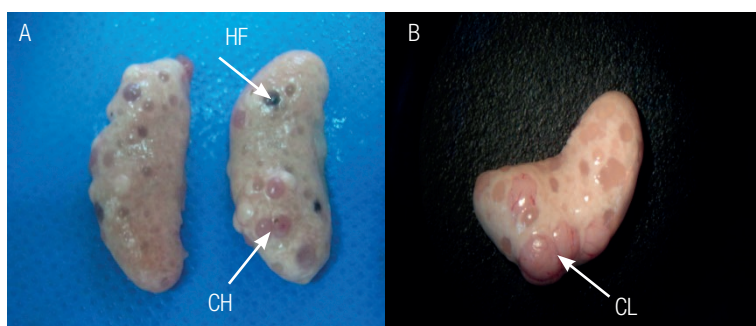
### **Body condition**

The weight of the female is an essential condition for the start of the ovulatory process. The relationship between ovulation rate and body weight of the female is positive (Khalil *et al.*, 1986; Blasco *et al.*, 1992; Peiró *et al.*, 2019), with an increase between 1 and 1.3 ova for each 250 g increment of body weight (Hulot *et al.*, 1982; Matheron and Poujardieu, 1982). Recently, a quadratic relationship between body weight at mating and ovulation rate has been found (García *et al.*, 2021). Thus, depleted body weight or being overweight have a negative effect on ovulation rate.

When body condition is measured as perirenal fat thickness, a linear and negative relationship between ovulation rate and perirenal fat thickness has been found (García *et al.*, 2021). Nevertheless, ovulation rate and ovulation frequency are not affected by body condition when measured as body condition score (Cardinelli *et al.*, 2008), although in this study it is necessary to consider that ovulation was induced by injection of 10 µg of synthetic Gonadotropin Releasing Hormone (GnRH).

### **Receptivity**

Receptivity is related to a high number of preovulatory follicles on the ovaries (Marongiu and Dimauro, 2013), and consequently a high concentration of estradiol (Rebollar *et al.*, 1992). In natural mating, ovulation seems to be conditioned by the receptivity of the female rabbits at the time of mating (Theau-Clément, 2008). In fact, females that



**Figure 1:** Rabbit ovaries with stigma ovulation at 72 h (A) and *corpora lutea* at 12 d *post coitum* (B). CH: *Corpora haemorrhagica*. HF: Haemorrhagic follicles. CL: *corpora lutea*.

accept mating have a greater number of preovulatory follicles compared to those that refuse (Lefevre *et al.*, 1978). Similarly, in artificial insemination, Theau-Clément *et al.* (2000), point out that receptive females respectively have a higher number of preovulatory follicles (14.3 vs. 9.4), ovulate more frequently (99.2 vs. 80%), have a higher number of *corpora lutea* (12.2 vs. 9.7) and segmented ova (11.2 vs. 4.8) compared to non-receptive females.

### **Parity order**

Ovulatory potential in rabbits improves with age and parity of the female. Primiparous and multiparous females have respectively 1.55 and 2.42 more *corpora lutea* than nulliparous females (Hulot and Matheron, 1981). Moreover, Zerrouki *et al.* (2009) indicated that the increase in ovulation rate observed with advanced of female mating is smaller between the first two matings. Nevertheless, Vicente *et al.* (2022) has showed similar ovulation rates in nulliparous and multiparous New Zealand White females (16.6 vs. 15.1 *corpora lutea*, respectively). On the other hand, nulliparous females ovulate more frequently than primiparous and multiparous females (on average, +20%) (Hulot and Matheron, 1981; Bolet *et al.*, 1996).

### **Reproductive rhythm and lactation**

The reproductive rhythm affects the ovulation rate, which is generally lower in females mated at 48 h *post-partum* (-16.5%) compared to those mated at 10 d *post-partum* (Selme and Prud'hon, 1973). The relationship between reproductive rhythm and ovarian status was also studied by Theau-Clément *et al.* (2000). These authors reported that does mated one day after parturition are very receptive (97.5%) but have a low number of unruptured follicles (8.8 follicles). However, at 4 d *post-partum*, females are less receptive (70.3%), and have a low ovulation rate (10.1, *corpora lutea*) and a high number of unruptured follicles (16.3 follicles).

In literature, data concerning the effect of lactation on ovulation are often contradictory. In lactating females compared to non-lactating females, ovulation is delayed and the ovulation rate is low (Fortun and Bolet, 1995). However, Mocé *et al.* (2002) found an increase in ovulation rate of 10.2% in lactating rabbits while Fortun Lamothe *et al.* (1999) and Juárez *et al.* (2021) found no effect of lactation on ovulation rate. Divergence in results between authors can be explained by the use of different lines, reproduction rhythm, food and seasons.

The hormonal status of the lactating female is different from that of the non-lactating female, with high levels of prolactin (McNeilly and Friesen, 1978) and oxytocin (Fuchs *et al.*, 1984) and low levels of progesterone (Fortun-Lamothe *et al.*, 1993), which explains the effect of lactation on ovulation.

Furthermore, hyperprolactinemia may explain a large part of the effect of lactation on ovulation (see review of Fortun-Lamothe and Bolet, 1995). Muelas *et al.* (2008) reported that females with higher ovulation rate have lower plasma concentrations of prolactin than females with lower ovulation rate (2.4 vs. 1.7 ng/mL). Prolactin is secreted in large quantities during the lactation period by the pituitary gland and by extra-pituitary sites such as the mammary gland, placenta and uterus (Ben-Jonathan *et al.*, 1996; Ubilla *et al.*, 2000). Prolactin secretion fluctuates with the stage of lactation and directly influences the follicles of the rabbit and modulates their growth (Djiane and Durand, 1977; Ben-Jonathan *et al.*, 1996). Moreover, the existence of prolactin receptors in rabbit ovary suggests that this hormone has a direct effect on follicular development and oocyte quality (Torner *et al.*, 2001).

### **Feed and nutrition status**

Interaction between nutrition, physiology and reproductive performances of the does was reviewed by Parigi-Bini and Xiccato (1993). It was reported that an altered maternal nutritional regimen prior to mating can influence follicular characteristics and embryo development (MacLaughlin *et al.*, 2005; Daoud *et al.*, 2012).

Prolonged dietary restriction inhibits LH pulses and induces anoestrus by depressing GnRH pulses in the hypothalamus, which leads to decreased receptivity and fertility (Fortun-Lamothe *et al.*, 1999; Boiti *et al.*, 2008). Likewise, dietary restriction before or after puberty results in a reduction in the size and number of growing follicles (Fortun-Lamothe *et al.*, 2000) and a lower ovulation rate compared to females fed *ad libitum* (9.24 vs. 8 *corpora lutea*) (Hulot *et al.*, 1982). Similarly, prior to insemination, low nutritional status reduces ovulation rate and embryonic viability (Fortun-Lamothe and Gidenne, 2000).

According to Theau-Clément (2000), flushing after a period of restriction could improve the reproductive performances of young rabbits. Indeed, in 14-wk-old rabbits, a food restriction (70% of their intake) followed by a 4-d flushing doubled the number of antral follicles with a diameter greater than 0.6 mm.

On the other hand, acute feeding restriction results in lower leptin, 17 $\beta$ -estradiol (frequency and amplitude) and low peak LH (Brecchia *et al.*, 2006). Indeed, the role of leptin in ovarian function, embryonic development and embryo implantation has been suggested due to the presence of leptin receptors on granulosa, ovarian and oviduct cells (Cervero *et al.*, 2004; González *et al.*, 2006; Zerani *et al.*, 2004). Moreover, García *et al.* (2021) reported a negative relationship between leptin and ovulation rate, which could be related to the negative influence of elevated leptin levels on the ovarian function and oocyte quality (Smith *et al.*, 2002). Also, Hadjadj *et al.* (2021) have shown a positive correlation between ovulation rate and monounsaturated fatty acids in plasma measured at mating.

### **Season and photoperiod**

The season has a notable effect on ovulation rate (Wells *et al.*, 2016). Generally, the autumn season shows an adverse effect on it; e.g. Pilawski (1969) and Selme and Prud'hon (1973) reported a larger difference in autumn compared to spring (−3.9 and −2.8 ova, respectively). Summer and winter showed the highest ovulation rate (14.9 and 13.8 *corpora lutea*), and autumn the lowest (13.4; García *et al.*, 2000).

### **Genotype and selection for ovulation rate**

The genetic type of the female has a significant effect on ovulation rate. The ovulation rate of Californian females is higher than that of New Zealand females (+2 ova), both breeds being selected for litter size at weaning (Torres *et al.*, 1987). In addition, Ragab *et al.* (2014) reported differences in ovulation rate between four maternal lines (V, A, LP and H lines) of rabbits and their crosses showed significant heterosis. Paternal line (R line) shows similar ovulation rate (13.8 vs. 14.2 *corpora lutea*) but lower ovulation frequency than maternal line (70 vs. 86%). Ovulation frequency failures in R line could be due to deficiencies in follicular development affecting steroidogenic activity or LH receptors, an inadequate neuroendocrine reflex at hypothalamus-pituitary system as a consequence of oestrogen insensitivity or a low bioavailability of steroids (Vicente *et al.*, 2012).

Heritability of ovulation rate ranges from 0.16 to 0.44 (Ibáñez *et al.*, 2006) (and is positively correlated with litter size (+0.56) (Blasco *et al.*, 1993a; Bolet *et al.*, 1994; Ibáñez *et al.*, 2006; Laborda *et al.*, 2011), therefore it was proposed as an indirect way to improve litter size at birth (Blasco *et al.*, 1993b). An experiment selection programme for ovulation rate in rabbit was performed at the Universitat Politècnica de València. Laborda *et al.* (2011) reported an increase in ovulation rate (+1.32 oocytes) after 10 generations of selection, but there was no correlated response on litter size (−0.15 kits). The response to selection was relevant, but it did not modify litter size because of an increase in prenatal mortality.

Another experiment for two-stage selection for ovulation rate and litter size was carried out (Ziadi *et al.*, 2013). After 7 generations of selection, the ovulation rate and litter size increased by 1 ova and 0.9 kits, respectively. Moreover, the number of young rabbits at slaughter was improved without modifying survival from birth to slaughter (Badawy *et al.*, 2019). Peiró *et al.* (2019 and 2021) reported positive genetic correlations between ovulation rate and growth traits (weight at 28 d, + 2.3 g/generation; weight at 63 d, + 11.2 g/generation; growth rate, + 7.9 g/generation). However, the correlated response on the variability of growth traits was close to zero.

When the selection criterion is litter size at weaning, the correlated response to selection on ovulation rate depends on the line. Thus, V line shows a positive correlated response (0.18 ova per generation, García and Baselga 2002a), while A line has not changed its ovulation rate (García and Baselga, 2002b). No response in ovulation rate has been obtained in lines selected divergently for litter size variability either (Calle *et al.*, 2017 and Argente *et al.*, 2017).

## **PRENATAL SURVIVAL**

Prenatal survival is the proportion of ova represented by neonates at birth. However, litter size is far from being identical to the number of ova shed. This variation is related to prenatal losses that occur during the different phases

of gestation. In rabbit, approximately, 17-40% of oocytes released during ovulation do not arrive at delivery (Adams, 1962; Santacreu *et al.*, 1990; Theau-Clément *et al.*, 2000; Vicente *et al.*, 2013; Belabbas *et al.*, 2021).

Prenatal survival can be divided into two periods: embryonic and foetal. Embryonic period corresponds to losses before implantation at 7<sup>th</sup> day *post coitum*, and is estimated as the proportion of implanted embryos from the number of *corpora lutea*. The foetal period, corresponding to the period from implantation to birth, is estimated as the proportion of kits born from the number of implanted embryos. Prenatal survival is thus estimated as the proportion of kits born from the number of *corpora lutea* (Mocé and Santacreu, 2010; Ragab *et al.*, 2014).

Mortality in the preimplantation period varies between 10 and 21% (Torres, 1982; Santacreu *et al.*, 1990), but differences can be observed between different lines (Bebin *et al.*, 2016). During this phase, losses are mainly related to embryo viability (chromosomal abnormalities, oocyte and embryo development) (Scofield, 1972; Pope *et al.*, 1990), and to the uterine and oviductal environment (composition of uterine secretions) (Torres *et al.*, 1987; Bazer *et al.*, 1990; Fayos *et al.*, 1994).

After implantation, there are three critical periods described for foetal mortality. The first is between 8 and 17 d of gestation, when the haemochorial placenta completes its development and foetal nutrition begins to come under the control of the placenta. During this period, the foetuses are not affected by the uterine capacity of the female (Adams, 1960, Figure 2). Losses during placentation are 2% (Torres, 1982). The second period is observed between 17- and 24-d *post coitum*, corresponding to the period of uterine elongation when tension on the spherical conceptus is at its maximum and blood flow to the uterus decreases (Figure 3). Fatal losses observed during this period appear to be related to placenta development (Hafez and Tsutsumi, 1966; Argente *et al.*, 2003a), which is itself influenced by the availability of space or uterine capacity of the female (Mocé *et al.*, 2004) and by vascularisation of the uterus (Duncan, 1969; Argente *et al.*, 2008). The foetal mortality in this period varies between 20 and 22% (Santacreu *et al.*, 1992, 2000; Garcia *et al.*, 2000; Belabbas *et al.*, 2021). Adams (1960) and Argente *et al.* (2008) found that 66 and 27% of total foetal losses are observed between implantation and day 17 of gestation and between day 18 and 24 of gestation, respectively. Finally, the third period occurs during the last week of gestation when energy requirements for foetal growth increase rapidly, while food intake decreases in the days before delivery (Fortun-Lamothe, 2006).

### Factors affecting prenatal survival

#### Oocyte quality and uterine environment

Embryonic survival depends mainly on the viability of the embryos, the oviductal and uterine environment. Several glycoproteins and proteins in the oviduct and uterine fluid, such as oviductin or uteroglobulin, have an important role for embryo survival, as they are related to sperm capacitation, fertilisation, blastocyst development and embryo implantation (Nancarrow and Hill, 1995; Buih and Alvarez, 2003; Killian, 2004; Beier, 2000; Merchán *et al.*, 2006, 2007).

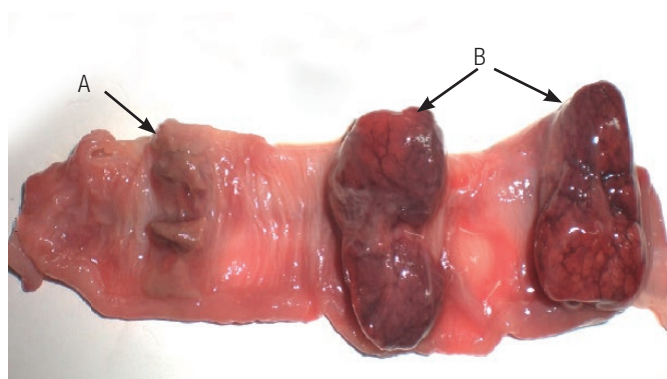
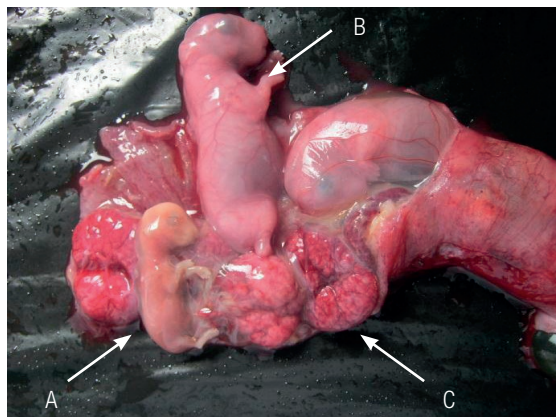


Figure 2: Post-implantation mortality in pregnant rabbit at 24 d. A: Resorbed implantation site without foetus. B: Maternal placenta of implantation site of developed foetus.



**Figure 3:** Foetal mortality in rabbit at 24 days of pregnancy. A: Dead foetus; B: Live foetus; C: Foetal placenta.

Furthermore, quantity and quality of uterine secretions, which vary from one female to another, have an effect on embryo implantation rates (Ulberg, 1974). Several metabolites including glucose, non-esterified fatty acids, hormones such as insulin and IGF1 regulate ovulation rate, follicular development and embryo survival (Ashworth *et al.*, 1999; Comin *et al.*, 2002; Ferguson *et al.*, 2003; García *et al.*, 2021; Hadjadj *et al.*, 2021). Also, leptin is involved as a key element in mammalian reproductive function (Cunningham *et al.*, 1999; Brecchia *et al.*, 2005; Alshaheen *et al.*, 2021).

The number of embryos that are able to implant also depends on the quality of the oocytes and duration of the ovulation process, leading to competition for embryos at different stages of development (Torres, 1982; Pope and First, 1985). Wintenberger-Torres *et al.* (1974) showed that poor quality embryos and less developed embryos can be implanted, although they will probably die later. Also, it was reported that embryonic development can be delayed by the disruption of proteins involved in embryonic growth under stress conditions (Puscheck *et al.*, 2015) or by genetic selection (Calle *et al.*, 2017).

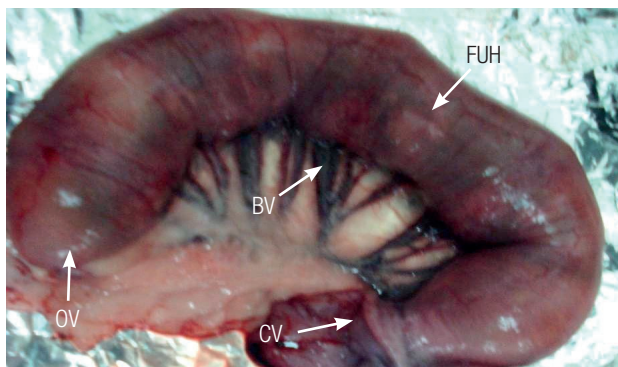
#### Parity order

Embryonic and foetal mortality tend to increase with parity order. Preimplantation mortality increases from 24 to 31% between nulliparous and primiparous stages and then to 38% at the multiparous stage. In contrast, post-implantation mortality shows a slight increase over the parities (6, 7 and 13% respectively in nulliparous, primiparous and multiparous rabbits) (Hulot and Matheron, 1981). Analysis of this parameter, at a constant number of *corpora lutea*, confirms this trend indicating defective implantation in multiparous females ( $-1.11$  implantation sites compared to nulliparous). The increase in mortality with age would be related to the deterioration in oocyte quality leading to fertilisation abnormalities or early embryonic mortality. This is essentially related to structural changes in the genital tract, manifested by deficient vascularisation and increased collagen content in the uterus, which could decrease the implantation rate (Finn, 1963).

#### Vascularisation, available space and uterine position

The relationship between prenatal mortality and *in utero* position can be explained by the available uterine space for each foetus on one hand, and the number of blood vessels reaching each implantation site on the other (Belabbas *et al.*, 2013; Argente *et al.*, 2008; Akkuşa and Erdogan, 2019) (Figure 4).

The vascularity of the implantation sites plays a key role in foetal survival and development. Indeed, the percentage of dead foetuses with a placenta receiving fewer than 3 blood vessels is higher than that of foetuses with a placenta receiving 3 blood vessels (Belabbas *et al.*, 2013; García *et al.*, 2021).



**Figure 4:** Uterine vascularisation of pregnant rabbit at 24 days of pregnancy. BV: Blood vessels reaching implantation sites; UH: Full uterine horn; OV: Oviductal extremity of the uterine horn; CV: Cervix.

Prenatal survival also depends on the available uterine space per foetus (Mocé *et al.*, 2004; Argente *et al.*, 2008). The probability of foetal survival increases with increasing of the available uterine space for each foetus, and can reach 90% from 4.5 cm of uterine space. In contrast, individual survival decreases in foetuses with little available uterine space (Argente *et al.*, 2006).

Furthermore, the intrauterine position also influences the percentage of foetal mortality. It is higher for foetuses in the cervical position compared to those in the oviductal and median position, related to less vascularisation (Argente *et al.*, 2006) and uterine space in this position (García *et al.*, 2021).

### Nutrition

Viudes-de-Castro *et al.* (1991) pointed out that the use of a high-energy diet does not lead to variations in the number of live embryos at 12 d of gestation, but to a significant decrease in the number of kits alive at birth (9.8 kits for the standard diet and 7.1 kits for the high-energy diet), which is related to a higher estimated foetal mortality for the energy diet (28 vs. 16%).

Undernutrition has a negative effect on foetal development (Lorenzo *et al.*, 1996). It is responsible for delaying embryonic development and increases mortality after fertilisation (Abecia *et al.*, 1997). In pregnant rabbit does, Menchetti *et al.* (2015) reported that undernutrition significantly reduces foetal adiposity, resulting in increased stillbirths due to failure of the thermoregulatory system and delayed postnatal growth.

Dietary deficiencies, particularly of vitamins A and E, can cause embryo degeneration or implantation failure (Boussit, 1989). Restricting the dietary level of young females during the rearing or gestation period reduces embryonic growth, increases foetal mortality and decreases the number of kits alive at birth (Naturil-Alfonso *et al.*, 2016). Similarly, dietary restriction during the gestation period tends to decrease the early survival rate (first half of gestation) (Fortun-Lamothe and Bolet, 1995). Likewise, dietary restriction of the pregnant rabbit is responsible for abnormalities expressed as abortions, reduced foetal weight and impaired ossification of developing foetuses (Nafeea *et al.*, 2011).

### Lactation

The effects of lactation on embryonic and foetal mortality are in contradiction. Higher mortality after implantation and during the second half of gestation in rabbits has been reported by García and Pérez (1989) and Fortun-Lamothe *et al.* (1993), while other studies show no effect (Partridge *et al.*, 1984; Juárez *et al.*, 2021). This may be related to the different reproduction rhythm used in these studies (mating immediately after parturition or at different periods of *post-partum*).

Foetal survival and development may be impaired when the rabbit is simultaneously pregnant and lactating. An increase in mortality occurs after day 15 of gestation, due to a large number of resorbed foetuses in lactating females

on day 28 of gestation (Fortun-Lamothe *et al.*, 1993). Two hypotheses can be put forward: either that the needs of the foetus are not met or that lactation induces an unfavourable hormonal environment for foetal development. In general, the energy balance of the female is negative during the second half of gestation, therefore the energy deficit is greater in pregnant and lactating females (Fortun-Lamothe *et al.*, 1999, 2006). This is particularly important in the rabbit, whose lipid reserves are low compared to other species (Ouhayoun *et al.*, 1986). The hypothesis of an energy deficit is plausible, as the lactation peak is observed approximately on day 15 of lactation when foetal mortality is recorded (Fortun-Lamothe, 2006). Moreover, the mammary gland and the foetal-placental unit use the same substrates, such as glucose, long chain fatty acids and free fatty acids (Jones and Parker, 1981; Fraga *et al.*, 1989; Stephenson *et al.*, 1990).

To limit the energy deficit, females have to simultaneously allocate the acquired resources to maintain their body and produce milk for the current litter, while the future litter is developing *in utero* (Garreau *et al.*, 2017). To meet their requirements, females increase their food intake, but this increase is insufficient, resulting in weight loss between days 14 and 28 of gestation. These losses are related to the mobilisation of body proteins and lipids (Castellini *et al.*, 2010).

Moreover, the level of progesterone must be sufficient to ensure a favourable uterine environment for the establishment and maintenance of pregnancy (Gadsby *et al.*, 1983; Lebas, 1994). Progesterone is secreted exclusively by the *corpora lutea* and its presence is necessary for pregnancy maintenance (Holt, 1989; Mocé *et al.*, 2002). The level of progesterone in the ovarian vein increases until mid-gestation and then decreases in the second half of gestation and drops rapidly before delivery. According to Fortun *et al.* (1993), the concentration of progesterone in the peripheral blood is lower in lactating primiparous females than in non-lactating primiparous females on days 7 and 17 of gestation, which is related to elevated prolactin levels (Lin *et al.*, 1987). This decrease in progesterone levels would be responsible in part for the increased foetal mortality observed in lactating females. Fortun-Lamothe and Bolet (1995) reported that the use of progesterone implants, from the seventh day of gestation, leads to a significant increase in the total number of foetuses at 28 d of pregnancy.

The rabbit female usually nurses her litter only once a day (Zarrow *et al.*, 1995) and stimulates prolactin secretion 15 min later. The concentration of prolactin is 10 to 20 times higher compared to the levels observed during gestation (McNeilly and Friesen, 1978). In general, this hormone affects embryonic viability, uterine function and its secretion during gestation (growth factors and uterine proteins) (Daniel *et al.*, 1988; Young *et al.*, 1989; Chilton and Daniel, 1987; Daniel *et al.*, 1989). Prolactin synthesis is dependent on lipoproteins which are also used by the mammary gland for milk production, thus reducing the availability of lipoproteins for ovarian steroidogenesis (Holt, 1989; Guesnet *et al.*, 1987).

Hyperprolactinemia has multiple effects involving specific mechanisms. Firstly, it can affect the relationship between the uterus and the foetus, altering epithelial cell differentiation, the quality of uterine secretions and ion transport across the epithelium (Chilton and Daniel, 1987; Daniel *et al.*, 1989). Secondly, it inhibits steroidogenesis in rabbits and consequently progesterone secretion (Lin *et al.*, 1987). Finally, lactation stimulates the secretion of oxytocin by the pituitary gland and as this hormone seems to have a luteolytic role it could therefore inhibit progesterone secretion (Fuchas *et al.*, 1984; Flint *et al.*, 1986; Sawyer *et al.*, 1986). Moreover, Argente *et al.* (2014) reported higher levels of plasma cortisol in lactating females compared to non-lactating females. This hormone inhibits proliferation and promotes cell differentiation and can affect placental development (Hewitt *et al.*, 2006).

Furthermore, according to Mocé *et al.* (2008), foetal viability depends on proteins secreted by the uterus, the main one being uteroglobin. Uteroglobin seems to play an important role at implantation, as the peak of secretion is observed at this stage. Jänne (1981) showed that a low estradiol concentration increases the effect of progesterone on uteroglobin secretion, whereas a high dose reduces the action of progesterone on uteroglobin secretion, which increases embryonic mortality.

### Temperature and season

Heat stress could provoke an unfavourable energy and/or endocrine balance in does, increasing the failures during gestation (Vicente *et al.*, 2012). A higher temperature (30°C and above) on the day of mating and in the following days affects pre- and post-implantation mortality (Boussit, 1989) as a consequence of lower embryo development



(García and Argente, 2017). On the other hand, the conception rate seems to be related to the season. Ibrahim (1994) and Asker (1999) found a significant decrease in conception rate in summer and autumn compared to winter and spring. This reduction is thought to be related to reductions in ovulation rate (Dollah, 1990), fertilisation losses and/or early embryonic mortality (Marai and El-Kelawy, 1999), the number of implantation sites and the number of viable implanted embryos per female (El-Fouly *et al.*, 1997).

#### Genotype and selection for prenatal survival

Mortality during gestation varies according to genotype (Bolet and Theau-Clément, 1994). In Californian rabbits, 40% of ova fail to implant, compared to only 21% in New Zealand rabbits (Hulot and Matheron, 1981). Analysis of covariance with a constant number of ova, which allows a more accurate estimate for this mortality, confirms this difference between genotypes ( $-1.28$  implantation sites in the Californian rabbit compared to  $+1.28$  in New Zealand rabbits). Moreover, Vicente *et al.* (2012) reported that the difference in litter size between maternal and paternal Spanish lines is mainly related to difference in gestational losses, and highlighted that the embryo genotype influences foetal survival at day 25 of gestation. Vicente *et al.* (2013) reported that the genotype of the embryo and the female could affect prenatal survival. Recently, studies have shown that embryo genotype influences prenatal survival and foetal weight at early stages of gestation. However, placenta weight is affected by both female and embryo genotype throughout gestation (Naturil-Alfonso *et al.*, 2015).

The selection programme for ovulation rate and litter size carried out by Ziadi *et al.* (2013) showed correlated response to selection in prenatal survival. Specifically, prenatal survival increased 0.077 in generation 7 (around 2% per generation) and a small positive change in embryo and foetal survival was observed (approximately 0.020 in 7 generations). Thus, it seems that both embryo and foetal survival contributed with the same amount in the increase observed in prenatal survival (Ziadi *et al.*, 2013).

No correlated response on foetal and prenatal survival was found in V and A lines, selected for litter size at weaning (García and Baselga, 2002a; 2002b).

The divergent selection for litter size variability showed that a decrease in litter size variability showed a favourable effect on embryo survival and led to a higher litter size at birth (Argente *et al.*, 2017).

### UTERINE CAPACITY

Uterine capacity was defined by Christenson *et al.* (1987) as the maximum number of fetuses that a female is able to support at birth when ovulation rate is not a limiting factor. Uterine capacity has been directly related to prenatal mortality, as many embryos are resorbed between implantation and birth, related to the limitation in the uterine capacity (Hafez, 1966; Ford, 1997).

Limitation in uterine capacity is responsible for losses resulting from intrauterine crowding (Argente *et al.*, 2008). Therefore, selection for uterine capacity was proposed as an indirect criterion to improve prenatal survival and, consequently, litter size (Bennet and Leymaster, 1989). Two experimental divergent selections for increasing uterine capacity were performed in rabbits. They were made on the number of dead fetuses from implantation to birth (Bolet *et al.*, 1994) and litter size in unilateral ovariectomised females, which includes both embryo and foetal survival (Argente *et al.*, 1997). Selection for uterine capacity has increased litter size but does not seem to be more effective than direct selection for increased litter size (Santacreu *et al.*, 2005). Low estimated response found in uterine capacity was in agreement with low estimated heritability, around 0.10 (Bolet *et al.*, 1994, Blasco *et al.*, 2005). This could be related to higher mortality, especially before implantation (Mocé *et al.*, 2004). Argente *et al.* (2003b), in complex segregation analysis found evidence of major genes with a moderate effect on uterine capacity and a large effect on number of implanted embryos.

### CONCLUSION

In conclusion, environmental and genetic factors affecting ovulation rate and prenatal mortality were studied. These components are mainly affected by the physiological and hormonal status of the female, feed composition,

management and season. On the other hand, ovulation rate that presents higher heritability was proposed as an indirect selection criterion for improving litter size. This selection was relevant, but did not modify litter size due to an increase in prenatal mortality. Different correlated responses in litter size components have been found when selecting for the mean or the variance of litter size.

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