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PAPER

Recipient maternal genotypes improved the litter size components of a paternal line involved in a MOET programme in rabbits

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ABSTRACT

An essential factor in the success of multiple ovulation and embryo transfer programmes (MOET) in any species is the selection of the recipient females. In rabbit there is a notable lack of studies on the effects of recipient genotype on postnatal growth. The aim of this study was to evaluate the effects of recipient maternal genotypes on litter size components within a MOET programme applied to a commercial paternal line that appears to have exhausted its selection programme after 37 generations. The experiment was designed using 13 nulliparous donors from the R line (paternal line) to produce 453 embryos, which were transferred to two recipient maternal genotypes (A and V lines) and the own donor paternal line (R line). Litter size components and pre-and postnatal body mass of kits were evaluated. The differences between the genetic groups of recipients were estimated using a general linear model applying Bayesian analysis. The results showed that maternal lines have a high capacity to implant the embryos, maintain the pregnancy and present a favourable environment for embryo development compared to the R line. Specifically, A line dams showed the highest prenatal survival, total born and number born alive without effects on growth traits. The present study demonstrated the applicability of a MOET programme based on maternal ability recipients to improve the number of kits per cycle. Therefore, to allow the genetic improvement programme of meat rabbits to continue using the R line, we recommended applying for a MOET programme as a routine procedure.

HIGHLIGHTS

- MOET programme based on maternal ability recipients enhanced the number of kits per cycle.
- The MOET programme could be a routine procedure to favour the selection of paternal lines by increasing selection pressure.

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Superovulation; embryos; donor; recipient; breeding; growth traits

Introduction

Genetic improvement programmes for rabbits are usually organised in a pyramid scheme applying a three-way cross whereby selection nuclei, specialised maternal and paternal lines are selected for litter size and growth traits (Baselga 2004). In Spain, the nucleus of the "Universitat Politècnica de Valéncia" has maternal and paternal long-term selection schemes (Estany et al. 1989, 1992, Cifre et al. 1999; García and Baselga 2002; Sánchez et al. 2008; Ragab and Baselga 2011; Mínguez et al. 2016; El-Nagar et al. 2020). Notably, the paternal line selected for average daily gain during the fattening period, named R line (Baselga 2004), which has remained closed in the same selection nucleus and under the same selection and management programme since its foundation, recently reaching the 37th generation of selection (Juárez et al. 2021). Thus, the R line has a high growth rate and adult live weight, but presents a dramatically reduced reproductive performance. In comparison, this purebred line shows a high ovulation failure rate (30%) as a consequence of a reduction in LH release (Naturil-Alfonso et al. 2016), higher implantation losses (20–30%), gestational losses (50%), perinatal and lactation losses (Vicente et al. 2012; Juárez et al. 2021) and smaller litter size (Llobat et al. 2012; Vicente et al. 2012; Juárez et al. 2020, 2021). Indeed, it has recently

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been suggested that this line seems exhausted in terms of improving postweaning daily weight gain (Juárez et al. 2020). Disfavoured effects in behavioural, physiological, or immunological effects have been described when the selection was based solely on productive criteria (Rauw et al. 1998), such as reduced offspring survival (Leenhouwers et al. 2002; Su et al. 2007; Heuß et al. 2019).

In this context, one alleviation strategy to generate more animals to continue the selection process could be the use of a multiple ovulation embryo transfer (MOET) programme using recipients with high mothering abilities (Smith 1988). To the best of our knowledge, the use of a MOET programme in a rabbit genetic improvement programme has not been previously described. To ensure the success of a MOET programme, the management of the donor and recipient is critical, as donors are expected to produce good quality embryos and the recipients must be able to conceive the transferred embryo, maintain the pregnancy until full term and raise kits of high genetic merit (Lamb et al. 2016).

In a paternal line, to ensure the success of a MOET programme, knowing how features of the recipient can contribute to differences in birth mass is an essential predictor of postnatal development and life chances (Bautista et al. 2015). In the rabbit, the maternal effects play an essential role in several productive traits because the length of gestation is one month, and till the age of 3 weeks, kits feed only on their mother's milk, and weaning occurs at the age of 4 or 5 weeks (Szendrő et al. 2019). In mice, previous studies described significant effects of receptor genotypes on embryo survival and growth (Cowley et al. 1989; Pomp et al. 1989; Gilliam 2014), and maternal genotype has a more significant influence on embryo survival (Moler et al. 1980). In pigs, the recipient genotype does not affect the embryo survival but does affect embryo growth (Ashworth et al. 1990). In rabbits, several previous studies have highlighted the effect of receptor genotypes on embryo survival (Mocé et al. 2004; Vicente et al. 2013; Naturil-Alfonso et al. 2015). However, there have been few studies on the effects of recipient genotype on prenatal growth (Mocé et al. 2004; Vicente et al. 2013; Naturil-Alfonso et al. 2015). In particular, in rabbit there is a lack of studies on the effects of recipient genotype on postnatal growth, the period in which genetically superior animals will be selected for the next generation to accelerate rates of genetic gain.

On this basis, our study aimed to evaluate an alternative to increase the number of animals of the R line through a MOET programme, seeking to increase survival through mothering abilities (maternal genetic effects) of recipients without altering the average daily gain during the fattening period.

Materials and methods

Animals

Three commercial purebred lines were used in this experiment; one paternal line (R line, donor and recipient, California origin) selected for the average daily gain during the fatting period (Estany et al. 1989), and two maternal lines (A and V lines, recipients, New Zealand origin) selected for litter size at weaning (Ragab and Baselga 2011). In order to have uterine environmental effects as the only source of variation, all the donors were nulliparous animals of the R line, with a body mass of around 4.5 kg. In addition, all the recipient genotypes were non-lactating multiparous animals. Animals were housed individually in flat cages and reared under the same conditions of photoperiod (16 h light and 8 h of darkness) with ad libitum access to water and feeding (commercial diet).

Experimental design

Figure 1 illustrates the experimental diagram. A total of 453 embryos were recovered from 13 donor females of line R, and sibling embryos were equally divided and transferred to the recipient genotypes.

Embryo production

Donor animals were subjected to superovulation treatment by subcutaneously administering with 3 μg of follicle-stimulating hormone corifollitropin-α (Elonva, Merck Sharp & Dohme B.V., Viudes-de-Castro et al. 2017). Seventy-two hours later, they were inseminated with 0.5 mL of a heterospermic pool of fresh diluted semen with proved fertility. At the time of artificial insemination, 1 μg of buserelin acetate (Hoechst Marion Roussel S.A., Madrid, Spain) was administered to induce ovulation.

Embryo collection

At seventy-two hours post-insemination, animals were euthanised and embryos were collected by flushing each oviduct and uterine horn with 5 mL of pre-warmed basal medium (BM), which contains 10% v/v Dulbecco's phosphate-buffered saline (Cytiva) supplemented with 0.2% w/v bovine serum albumin (Fisher

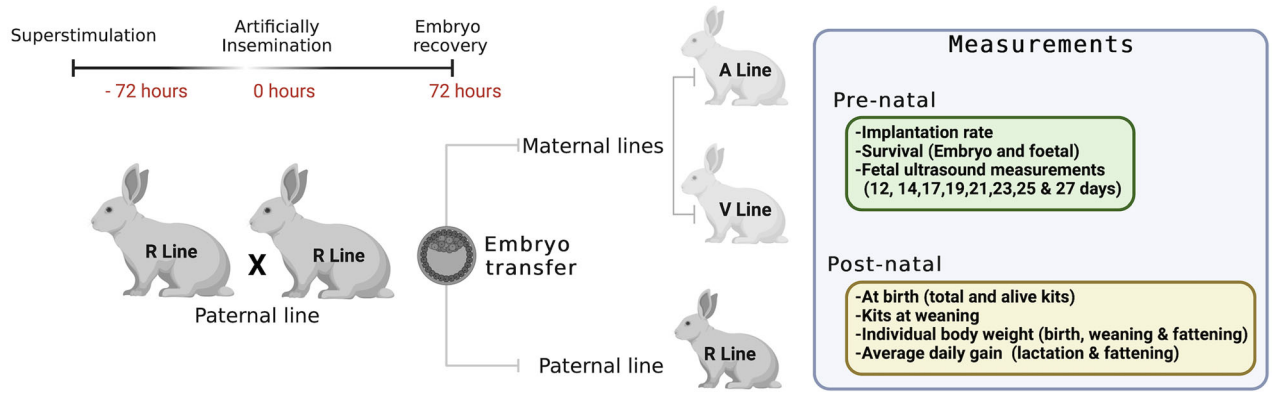

Figure 1. Overview of the study design. Line R females (paternal line) selected for the average daily gain during the fatting period were superstimulated using a single injection of long-acting corifollitropin supplemented with human chorionic gonadotropin. Seventy-two hours later, the females were artificially inseminated and euthanised 72 h later. Then, embryos by donor were collected and equally transferred into two maternal lines (A and V lines) selected for litter size at weaning and the own R line. Litter size components (pre-and postnatal) and body growth traits (pre-and postnatal) were evaluated.

Scientific) and 1% v/v antibiotics (10,000 U/mL Penicillin, 10,000 µg/mL; Gibco) as described by Vicente et al. (2013). After recovery, embryos catalogued as morphologically normal morulae and blastocysts (intact mucin coat, spherical zona pellucida and homogeneous cellular mass) were washed twice in fresh BM. Thirteen donors were used, since they produced from 21 to 42 embryos catalogued as ideal for transfer. Thus, an equal number of sibling embryos between 7 and 14 was transferred to each recipient line.

Embryo transfer

Receptive females were induced to ovulate by a single intramuscular injection of 1 µg of buserelin acetate 72 h before the transfer, as stated by Marco-Jiménez et al. (2013). Embryo transfer was performed as detailed by Garcia-Dominguez et al. (2019). Briefly, embryos were transferred into the oviduct *via* laparoscopy. The recipient does were anaesthetised intramuscularly with xylazine (5 mg/kg) and intravenously with ketamine hydrochloride (35 mg/kg), to finally be placed in Trendelenburg's position. An endoscopic trocar was inserted into the abdominal region and the peritoneal cavity was insufflated with a pressure-regulating mechanical insufflator to allow visualisation with the endoscope camera. An epidural needle was used to perforate the inguinal region. An epidural catheter is inserted through the needle and into the infundibulum to release the embryos in the oviduct. Equal numbers of embryos were transferred into the left and right oviduct of each recipient. A total of 151 embryos were transferred into each recipient genotype.

Prenatal development

Twelve days after ovulation induction, recipients were anaesthetised as previously and examined by embryo transfer procedure. Then, the number of implanted embryos (IE) was recorded. From ET and IE, the embryo survival (ES) was calculated (IE/ET). On the day of parturition, the total number born (TB), number born alive (NBA) and number born dead, foetal survival (FS; calculated as TB/IE), and prenatal survival (PS; calculated as TB/ET) were determined.

Foetal growth study

Foetal growth was examined at days 11, 13, 15, 18, 20, 22, 25 and 27, by a portable colour Doppler ultrasound device (Esaote, Spain) with 7.5-MHz linear probe (4–12 MHz range). The ultrasound examination was performed from right to left with the probe in sagittal orientation and, after the localisation of different foetal areas, 5–7 foetal sac examinations per doe were performed. The identifiable structures (foetal sac, foetus, and foetal and maternal placenta) were measured using Esaote 16 ultrasound software. Foetal growth was determined as the maximum distance from the crown to tail basis with the foetus on a sagittal plane. The ultrasound examination was performed according to the procedure described by Vicente et al. (2013).

Postnatal growth performance

Body mass was annotated at birth, at weaning (4 weeks) and at the end of the fattening period (9 weeks). In addition, the growth rate was estimated as the average weight gain (ADG) between the fourth

and ninth week, the standard criterion for selecting rabbits in paternal lines (de Rochambeau et al. 1989; Estany et al. 1992; Gómez et al. 2002).

Statistical analysis

All traits were analysed using a general linear model, assuming that, in general, all traits are mainly determined by the genotype of the recipients. Our experiment was carried out in the same year-season and all the recipients had similar body mass, age, physiological state (multiparous non-lactating does) and similar production conditions (equal parity number). To analyse foetal sac area, crown-rump length of foetus, foetal and maternal placenta areas at different days of gestation, litter size traits at birth (TB and NBA) and weight of liveborn kits and number of implanted embryos were used as a covariate and common litter as a random effect.

Descriptive statistics, phenotypic contrasts between different recipient genotypes and the probability of the estimated contrast being greater than 0 when A-$R > 0$ were computed with the Rabbit software program developed by the Institute for Animal Science and Technology (ICTA, Valencia, Spain). After some exploratory analyses, results were based on Markov chain Monte Carlo chains consisting of 60,000 iterations, with a burn-in period of 10,000, and only 1 of every 10 samples was saved for inferences.

Results

The total number of recipient dams and young rabbits after parity, with their means and standard deviations of the considered traits, are presented in Table 1. The results showed a prenatal survival rate of 44%, with an average of 6.9 embryos implanted and 5.2 kits born. Offspring rate at birth was 75.4% from implanted embryos. The ADG was 51.4 g between the weaning and fattening period (63 days from 4 to 9 weeks of age). In order to rule out the effects of the MOET programme, the ADG was determined in line R animals coetaneous with the selected population, this value being 50.9 g, which implies that the MOET procedure did not affect growth.

The contrasts and probability of the contrast being higher than 0 ($p > 0$) between recipient genotypes for litter size and its components are presented in Table 2. Important differences were observed between the recipient genotypes. Both maternal lines (A and V lines) showed a higher number of implanted embryos compared to the R line (1.22 and 1.06, favouring lines A and V respectively). Moreover, our results indicate the presence of a significant maternal genetic effect on embryo survival with important differences (7.41% and 8.00%, for A and V lines, respectively) and prenatal survival (7.25% and 6.95%, for A and V lines, respectively). However, the maternal effects were not relevant on the foetal survival rate. For the litter size parameter, significant effects of recipient genotype were observed, with the largest TB exhibited by lines A and V (increasing offspring per birth by 1.44 and 1.02, with a likelihood of these differences being greater than zero of 80% and 89% for lines A and V,

Table 1. Number of data (*n*), raw means and standard deviation (*SD*) for litter size components and growth traits.

Traits	*n*	Mean	*SD*	Minimum	Maximum
EI	39	6.9	3.5	0	14
ES (%)	39	59.1	28.2	0	100
FS (%)	39	64.2	32.9	0	100
PS (%)	39	44.3	28.1	0	92
TB	37	5.2	3.5	0	12
NBA	37	4.0	3.2	0	11
NW	37	3.7	2.2	0	9
BW0 (g)	150	68.7	16.1	28	105
BWW (g)	138	640.1	160.1	250	1050
BWS (g)	130	2446.2	354.43	1490	3350
ADG-LAC(g)	138	20.4	5.3	7.3	34.3
ADG (g)	130	51.4	7.2	27.5	70

EI: number of implanted embryos; ES: embryo survival; FS: foetal survival: PS: prenatal survival; TB: total born; NBA: number born alive; NW: number weaned; BW0: individual kit body weight at parity; BWW: individual body weight at weaning; ADG-LAC: Average daily gain during lactation period (0–4 weeks); ADG: Average daily gain during the fattening period (4–9 weeks).

Table 2. Features of the estimated marginal posterior distributions of the differences between the recipient genotypes for litter size components and their variability.

Trait		A-R	$HPD95_{\%}$	*p*	V-R	$HPD95_{\%}$	*p*	A-V	$HPD95_{\%}$	*p*
Implanted embryos		1.22	−1.37, 3.56	0.84	1.06	−1.2, 3.49	0.81	0.16	−2.29, 2.76	0.55
Survival (%)	Embryo	7.41	−13.08, 27.10	0.77	8.00	−12.18, 29.07	0.79	−0.59	−22.48, 20.34	0.48
	Foetal	5.06	−17.90, 29.27	0.66	2.29	−22.55, 28.55	0.59	2.77	−21.06, 27.08	0.57
	Prenatal	7.25	−12.97, 27.51	0.77	6.95	−12.9, 27.70	0.77	0.30	−21.33, 20.73	0.51
Kits at birth	Total	1.44	−0.94, 3.82	0.89	1.02	−1.31, 3.44	0.80	0.42	−2.19, 2.82	0.62
	Alive	1.54	−0.62, 3.67	0.92	1.10	−1.23, 3.21	0.83	0.44	−1.70, 2.87	0.65
Kits at weaning		0.09	−1.73, 1.74	0.55	0.85	−1.11, 2.54	0.83	−0.76	−2.62, 1.11	0.21

A: Line A. Maternal line selected for litter size at weaning (4 weeks). R: Line R. Paternal line selected for average daily gain during the fatting period litter (4–9 weeks). V: Line V. Maternal line selected for litter size at weaning (4 weeks). HPD95%: highest posterior density region at 95%. *p*: probability of the difference between the control and selected population being higher than zero.

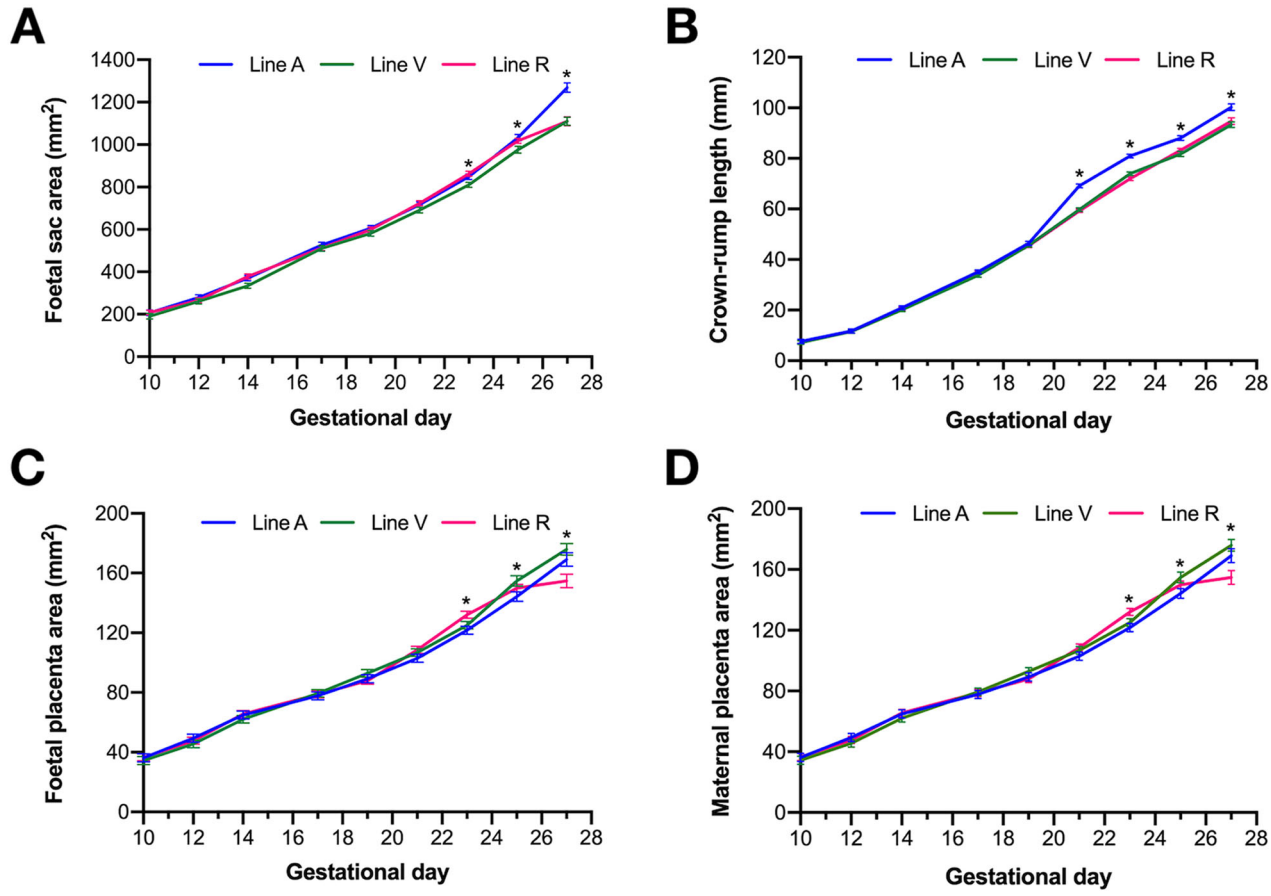

Figure 2. Foetal ultrasound measurements (foetal sack, crown-rump length and the foetal and maternal placenta) during pregnancy to compared the effect of recipient genotype in a MOET protocol in a commercial rabbit parental line. A: Line A. Maternal line selected for litter size at weaning (4 weeks). R: Line R. Paternal line selected for average daily gain during the fatting period litter (4–9 weeks). V: Line V. Maternal line selected for litter size at weaning (4 weeks). *Values for each ultrasound measurement and gestational day with asterisk are statistically different ($p < 0.05$).

Table 3. Features of the estimated marginal posterior distributions of the differences between the recipient genotypes for growth traits and their variability.

Trait		A-R	HPD95%	*p*	V-R	HPD95%	*p*	A-V	HPD95%	*p*
Individual body weight (g)	Birth	−7.65	−18.8, 2.9	0.08	2.78	−7.6, 13.7	0.69	−10.43	−20.3, 0.2	0.08
	Weaning	−62.11	−212.6, 79.5	0.19	−8.20	−156.5, 134.0	0.45	−53.90	−187.1, 80.3	0.21
	Fattening[1]	24.32	−279.4, 345.4	0.57	22.79	−277.6, 343.2	0.56	1.53	−281.9, 307.7	0.51
Average daily gain (g)	Lactation	−2.03	−6.85, 2.5	0.2	−0.48	−5.3, 4.23	0.42	−1.55	−5.86, 3.35	0.24
	Fattening[2]	2.05	−3.92, 7.92	0.76	0.88	−5.1, 6.58	0.62	1.19	−4.10, 6.91	0.66

A: Line A. Maternal line selected for litter size at weaning (4 weeks). R: Line R. Paternal line selected for average daily gain during the fatting period litter (4–9 weeks). V: Line V. Maternal line selected for litter size at weaning (4 weeks). HPD95%: highest posterior density region at 95%, P: probability of the difference between the control and selected population being higher than zero. Birth: individual body mass at parity. Weaning: individual body mass at weaning (4 weeks). Fattening: individual body mass at fattening (9 weeks). Lactation: Average daily gain between 0 and 4 weeks. ADG: Fattening[2]: Average daily gain between 4 and 9 weeks.

respectively). Meanwhile, the use of the R line as a recipient was unfavourable for NBA, where the mortality at birth was higher than in the other lines, where the A and V recipients showed a high mean value of NBA (1.54 and 1.10 for the A and V lines, respectively). Moreover, high mortality during the lactation period leads to reduction of the NW obtained by line A, while the recipients of line V showed relevant differences compared to the recipients of A and R lines, with (0.76 and 0.85 kits per parity, respectively).

Regarding the prenatal growth of embryos, the recipient genotype has significant effects (Figure 2). In the first days of gestation, there were no differences between traits, but on day 20 and 25 of gestation, the A line showed a higher foetal length (Figure 2) and higher foetal placenta area and foetal sac area compared to other lines. Regarding the maternal placenta area, there are no relevant differences between lines.

Regarding the postnatal growth of kits, at birth, progeny derived from line V recipients provided

higher body mass (2.78 g, with $p > 69\%$, Table 3). No significant effect was observed between recipients for the ADG during the lactation, but during fattening, recipients from line A showed slightly higher ADG than progeny produced by recipients R and R (2.05, 1.19 g/days, respectively, Table 3), although this does not appear to be relevant.

Discussion

This study demonstrated a clear relationship between recipient female genotype and survival, without effect on body mass at all life stages until selection. Consistent with this, we report that a MOET protocol allows a tripling of the number of offspring per cycle in each mating and could therefore be applied as a routine procedure to follow the selection of this terminal purebred beyond the current generation 37.

Broadly, intensive rabbit production involves a three-way cross in which males selected for growth traits from paternal lines are mated with crossbred females from lines selected for reproductive traits (Baselga 2004). Thus, for rabbit breeding programmes, purebred paternal lines in nucleus units should have adequate reproductive traits to ensure line maintenance and selection over time (Peiró et al. 2021). Due to the fact that the R line has a low reproductive efficiency that is based on ovulation failures, high embryonic and foetal losses and during the lactation period (Llobat et al. 2012; Vicente et al. 2012; Juárez et al. 2020, 2021), which has highlighted possible exhaustion of selection after 37 generations (Juárez et al. 2020), we applied the MOET technology to produce embryos from R donors that were transferred to maternal lines with superior mothering abilities to increase the number of genetically superior animals for the next generation and to be able to increase the selection pressure in order to enhance the genetic gain (Mueller and Van Eenennaam 2022). Our results demonstrate an improvement in pre-and postnatal survival when maternal lines are used as recipient mothers, consistent with previous findings in a reciprocal embryo transfer study (Naturil-Alfonso et al. 2015). Moreover, the superior mothering abilities of the A line compared with other maternal lines have been well documented, where this line provided a high capacity to maintain the embryos during the pregnancy (Ragab et al. 2014). This expected result illustrates the improvement in mothering abilities after long-term selection by litter size at weaning (Ragab and Baselga 2011), since the offspring's survival is controlled both by the genes of the animals that are involved in health, growth, etc. (direct genetic effects) and by the genes of the dam that affect mothering abilities (maternal genetic effects, Blasco et al. 1995). Other aspects of our results are consistent with previous findings on the R line, which indicate that the use of this paternal line as a recipient mother is associated with less survival, which again demonstrates the negative impact of selection for growth traits on reproductive traits in rabbit (Ernst et al. 2000; Lavara et al. 2008, 2011). In agreement with our results, in mice, Pomp et al. (1989) reported significant variation in embryo survival and prenatal growth among different recipient strains due to maternal uterine ability.

Regarding the high mortality during lactation observed in recipients of line A, this observation cannot be explained easily due to the high production level of this line, especially at weaning, as commented previously. This could be explained by González-Mariscal et al. (2013), who observed that suckling a few kits (less than 6) has unfavourable effects not only on nursing but also on the doe's behaviour in rabbits, which could lead to high mortality during the lactation period. Moreover, mortality during lactation could be associated with impaired maternal behaviour (Lavara et al. 2010). The result at weaning between recipients A and V could be in accordance with EL Nagar et al. (2014), which showed that V does have higher weekly milk yield traits than A, with a significant difference.

A successful MOET programme for selection purposes requires maximising superovulation response to achieve maximum efficacy (Rodríguez-Martínez 2012). In this way, our findings demonstrate the potential for tripling the number of siblings per cycle using a single injection of long-acting corifollitropin supplemented with human chorionic gonadotropin (Viudes-de-Castro et al. 2017, 2019), without any relevant effect on growth traits, using the dams of the maternal lines as recipients. Indeed, the comparisons between lines showed a similar average daily gain from 28 to 63 days of age, the standard criterion for selecting rabbits in paternal lines (de Rochambeau et al. 1989; Estany et al. 1992; Gómez et al. 2002). In rabbits, as in other altricial mammals, body mass at birth is closely associated with early postnatal survival and body mass at weaning (examples in Lummaa and Clutton-Brock 2002; Rödel et al. 2008, 2009; Hudson et al. 2011), which in turn, as in other species, is a good predictor of postweaning growth and survival (Murie and Boag 1984; Lenihan and Van Vuren 1996; Marboutin and Hansen 1998; Kraus et al. 2005; Rödel et al. 2015). Generally, a favourable environment during early life

positively affects individual growth and development (Rödel and von Holst 2009). In our study, the superior mothering abilities of maternal lines on survival were evident (Ragab and Baselga 2011). Furthermore, the importance of our findings can be extended not only to this parental line, but also to other lines, by allowing accelerated rates of genetic gain by increasing the number of animals per cycle in each mating.

Conclusion

Taken together, this study demonstrates that maternal genotypes as recipients increase the survival of embryos obtained in a MOET programme from a paternal line without affecting the body mass and average daily gain during the fattening period (standard criterion for selecting rabbits in paternal lines). Therefore, to allow the genetic improvement programme for meat rabbits to continue using the R line as a terminal sire, we recommended using a MOET programme as a routine procedure to follow the selection of this purebred line beyond the current generation 37.

Acknowledgments

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Ethical approval

The experimental protocol in this study was approved by the Ethical Committee for Experimentation with Animals of the Universitat Politècnica de València (code 2015/VSC/PEA/00061).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The original data of the paper are available upon request from the corresponding author.

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