



Does maternal size, nutrition and metabolic status affect offspring production traits in domestic species?

Morgane Robles, Pascale Chavatte-Palmer¹

UMR BDR, INRA, ENVA, Université Paris Saclay, 78350, Jouy en Josas, France.

Abstract

The Developmental Origins of health and Disease state that environmental conditions during pregnancy affect long term outcomes in offspring. In the present paper, effects of maternal size and breed as well as maternal nutrition on offspring size, growth and production traits are described. Although birthweight is mostly not affected, metabolic perturbations are often observed in adult offspring. In animal production, however, the relation between developmental conditions and long-term offspring outcome may remain unnoticed. Nevertheless, improving dams' health and nutrition before and during pregnancy may help improving production traits in domestic animals.

Keywords: DOHaD, embryo transfer, fetal programming, nutrition, pregnancy.

Introduction

In mammals, developmental conditions at the time of conception, during pregnancy and the neonatal period are known to affect long-term post-natal health, as known under the term “Developmental Origins of Health and Disease” (DOHaD). This phenomenon, is associated with modifications in gene expression due to environmentally induced epigenetic mechanisms. Maternal environment, such as maternal metabolism and nutrition, or the use of reproductive biotechnologies, may have an effect on fetoplacental development, growth and subsequent adult health, thus affecting offspring performance and longevity.

This article aims to summarize existing knowledge on long term effects of maternal phenotype in domestic species and their potential impact on animal health, fertility and welfare. Future directions both in research and for improvement of field management are discussed.

The other side of genetics: effect of maternal phenotype/genotype

Genetic selection for production traits is the basis of animal breeding. Taking into consideration maternal genetic value and production, the sire is selected based on his genetic indices and heritability, in order to improve desired production traits. Maternal genotype and phenotype are also seminal in determining the environment in which the embryo and fetus will develop, regardless of production traits. This can be

studied by comparing cross-bred offspring born to dams of different genotypes, or by studying phenotypic variation in genetically identical animals (Fig. 1).

In pigs, the cross-breeding between Meishan sows (200 kg adult weight) and Yorkshire males (300 kg adult weight) yields lighter piglets than the opposite crossing (Meishan males and Yorkshire sows; Biensen *et al.*, 1999). Similarly, in cattle, calves born to South Devon cows (790 kg adult weight) and Dexter bulls (340 kg adult weight) were approximately 6 kg heavier than crossbred calves born to a Dexter cow (Joubert and Hamond, 1958). Moreover, Charolais breed embryos transferred into Brahman cows are lighter at birth (mean 29 kg) compared to Charolais embryos transferred into Charolais recipients (mean 63 kg). Inversely, Brahman embryos transferred into Charolais recipients result in calves with heavier birthweight (mean 41 kg) than those produced by the transfer of Brahman embryos into Brahman cows (mean 19 kg; Ferrell, 1991). These results indicate that maternal breed and consequently maternal size and environment will affect offspring weight and size at birth, regardless of genetic potential.

Further consequences on postnatal development have been explored in horses. In the first half of the 20th century, Walton and Hammond elegantly demonstrated, using cross-breeding between large Shire horses and small Shetland ponies, that crossbred offspring whose dam was a Shetland pony were smaller at birth and remained smaller as adults than those whose dam was a Shire mare (Walton and Hammond, 1938). Almost 50 years later, Tischner *et al.* showed that Polish pony embryos transferred into draft mares produced foals that were larger at birth and remained larger as adults, compared to those that had been transferred into mares of their own breed (Tischner *et al.*, 2000). More recently, the transfer of pony embryos into mares of larger breeds was shown to consistently increase fetal and postnatal growth until adulthood. Conversely, foals from a larger breed born to pony mares were small at birth and only partially caught-up to controls of the same breed (Allen *et al.*, 2004; Peugnet *et al.*, 2014). Moreover, both excess and reduced fetal growth were associated with osteoarticular lesions and metabolic perturbations, some of which still present at 2 years of age (Peugnet *et al.*, 2014, 2016).

Effect of maternal nutrition

Procedures in terms of maternal nutrition in domestic animals vary greatly depending on breed, location, availability of feedstuff and season, amongst other factors. The choice of dietary treatments in

¹Corresponding author: pascale.chavatte-palmer@inra.fr

Phone: +33(1)3465-2558

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experimental protocols is also very diverse, rendering it difficult to draw clear conclusions. In general, the effects of maternal nutrition on offspring phenotype are marginal, except when dietary treatments are severe and prolonged as reviewed recently (Funston *et al.*, 2012;

Chavatte-Palmer *et al.*, 2015, 2016; Sinclair *et al.*, 2016; Opsomer *et al.*, 2017). The list of studies presented here does not claim to be exhaustive as the authors have selected key examples to illustrate each nutritional condition.

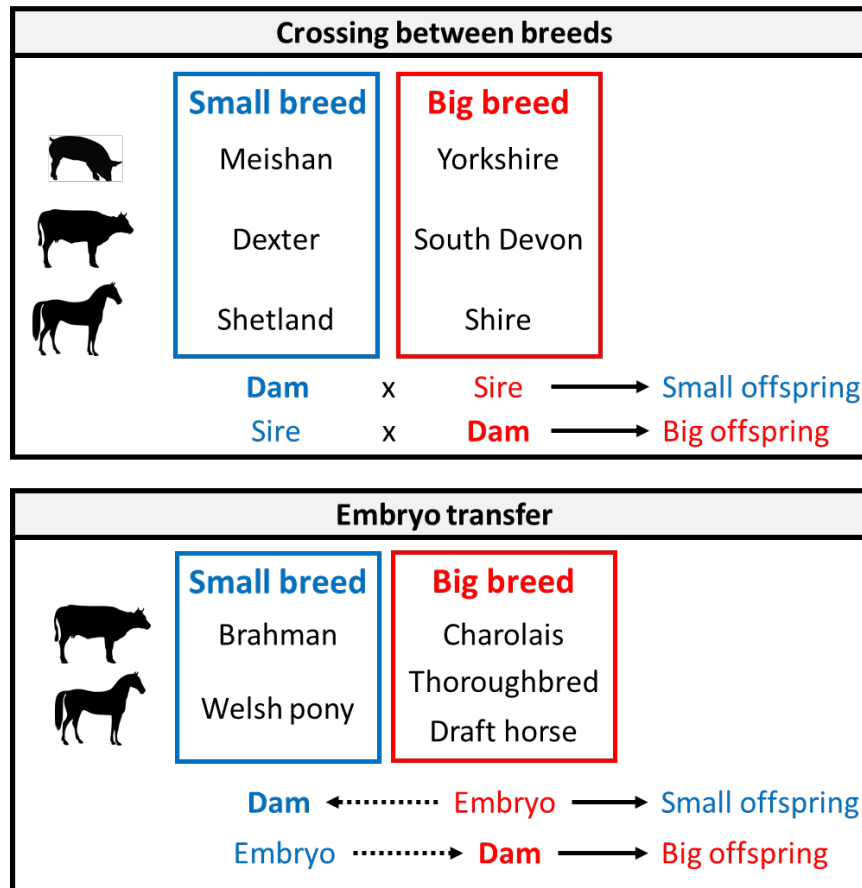


Figure 1. Effect of maternal and paternal size on offspring size after artificial insemination or embryo transfer. After Walton and Hamon (1938); Joubert and Hamon (1958); Ferrel. (1991); Biensen *et al.* (1999); Tischner *et al.* (2000); Allen *et al.* (2004); Peugnet *et al.* (2014).

Excess nutrition and obesity

In many studies, excess nutritional intake during pregnancy is confounded with maternal obesity. Obesity can be defined as excess adiposity above a certain level as defined by the authors depending on studies, before breeding and during pregnancy. Here we tried to discriminate studies with maternal gestational overfeeding from studies with maternal obesity prior to breeding.

Effects of excess maternal nutrition have been mainly studied in sheep (Table 1) with little observed effects on lamb birthweight and postnatal growth (Hoffman *et al.*, 2014; Khanal *et al.*, 2014; Kleemann *et al.*, 2015; Sen *et al.*, 2016). Nevertheless, expression of Insulin Growth Factor 1 (IGF1) is increased in the lamb liver (Hoffman *et al.*, 2014) resulting in increased plasma IGF1 concentrations (Hoffman *et al.*, 2016) and lipid accumulation is also observed in the lambs' muscle (Hoffman *et al.*, 2014; Reed *et al.*, 2014), together with increased insulin resistance (Hoffman *et al.*, 2016), increased adiposity (Khanal *et al.*, 2014),

hyperglycemia and alteration of hepatic signaling pathways (Philp *et al.*, 2008). Finally, increased ovarian size and reduced ovarian follicular numbers have also been observed (Da Silva *et al.*, 2003; Kleemann *et al.*, 2015). *Ad libitum* access to feedstuff at adulthood (19-22 months) increased food intake, weight gain, visceral and subcutaneous fat, basal glycemia and insulinemia in all animals but offspring born to obese dams were less affected than offspring born to control dams (Long *et al.*, 2010, 2015).

When maternal obesity was induced by overfeeding dams starting 2 months before breeding and until lambing, offspring birthweight was not affected but glucose metabolism was consistently and durably altered. The number of pancreatic β -cells was reduced in fetal life, resulting in hyperglycemia, unhyposulinemia and reduced pancreatic weight at birth and increased insulin resistance and altered glycemic regulation in adults. Moreover, muscular fibrosis and hyperleptinemia were observed (Long *et al.*, 2010, 2015; Huang *et al.*, 2012; Zhang *et al.*, 2012).



Table 1. Summary of studies performed on the effects of overnutrition in pregnant ewes on the post-natal development of the offspring. The level of excess nutrition is expressed as a percentage of the energy content ingested by the control group.

Level of overnutrition	Period of overnutrition	Function	Age	Phenotype	Source
Periconceptual overnutrition					
150%	From 17 days before insemination to 6 days after	Growth	Birth 5 days	= Live weight ↗ Ovary weight	Kleeman <i>et al.</i> , 2015
Overnutrition in the beginning of gestation					
<i>Ad libitum</i>	The 100 first days of gestation (2 first third)	Endocrinology Ovary function	103 days of gestation	↘ Progesterone concentration ↘ Number of primordial follicles ↘ Number of total follicles	Da Silva <i>et al.</i> , 2003
175%	From 30 to 80 days of gestation	Growth Muscle function	From birth to 5 months 5 months	= Live weight ↗ Fibres density	Sen <i>et al.</i> , 2016
Overnutrition in the end of gestation					
126%	From 116 days of gestation	Endocrinology	1 day	= Live weight ↗ Heart weight	Hoffman <i>et al.</i> , 2014
			3 months	↘ Live weight	
155%	From 115 days of gestation	Gene expression	From 1 day to 3 months	↘ IGFBP3 Concentration ↗ Leptin Concentration ↗ Liver <i>IGF1</i> expression ↗ Muscle <i>β-catenin</i> expression (stimulate the differentiation of stem cells into muscle cells) ↗ Fasting glycaemia	Philp <i>et al.</i> , 2008
		Carbohydrate metabolism	1 day	↘ % of phosphorylated AMPK in the liver (can contribute to ↗ the production of glucose by the liver)	
150%	From 105 days of gestation	Growth	From birth to 2 months	= Live weight	Khanal <i>et al.</i> , 2014
			From 2 to 6 months	↘ Live weight	
		Body condition	6 months	↘ % subcutaneous adipose tissue ↘ Subcutaneous adipose tissue / Visceral adipose tissue	



Level of overnutrition	Period of overnutrition	Function	Age	Phenotype	Source
Overnutrition during the most of gestation					
140%	From 31 days of gestation	Growth	From 1 day to 3 months 1 day	↗ Live weight, thoracic perimeter ↗ Length ↗ IGF1 Concentration	Reed <i>et al.</i> , 2014 Hoffman <i>et al.</i> , 2016 Pillai <i>et al.</i> , 2017
		Endocrinology	3 months	↗ IGFBP2 Concentration ↗ Leptin concentration	
		Carbohydrate metabolism	3 months	↗ Insulin/basal glucose ratio ↗ Insulin resistance	
		Muscle function	1 day 3 months From 1 day to 3 months	↗ Fibres area (cross section) ↗ <i>Myostatin</i> expression ↘ Fibres area (cross section) ↗ Lipid accumulation in muscle	
Modelling of obesity – Overnutrition throughout gestation					
150%	From 60 days before insemination	Gestation	Gestation length	↘ Gestation length	Long <i>et al.</i> , 2010 Huang <i>et al.</i> , 2012 Zhang <i>et al.</i> , 2012 Long <i>et al.</i> , 2015
		Growth	From birth to 19 months 135 days of gestation	= Live weight ↘ β pancreatic cells ↗ Production of insulin by remaining β cells	
		Carbohydrate metabolism	Birth 19 months	↗ Basale glycaemia ↘ Basale insulinemia ↘ Pancreas weight ↗ Insulin resistance ↘ Glucose disposition by insulin independent glucose transporters	
		Muscle function	2.5 years (males)	↗ Collagen concentration (=↗ fibrosis) ↘ Metalloproteases expression ↗ Metalloproteases inhibitor expression	
Endocrinology	2-3 years (males)	↗ Leptin concentration			

IGF1: Insulin Growth Factor 1; IGFBP3: Insulin growth Factor Binding Protein 3; AMPK: AMP-activated protein kinase; IGFBP2: Insulin growth Factor Binding Protein 2.

In order to understand the importance of preconceptional obesity, embryos produced in adult obese or control ewes were transferred in adolescent control or obese ewes (Wallace *et al.*, 2017). Pregnancy length was shorter in obese recipients and resulted in reduced lamb birthweight compared to controls, regardless of donor group. The colostrum quality was also affected by obesity (Wallace *et al.*, 2017).

Finally, in cattle, feeding with 125% requirements from 3 months of gestation increases calf birthweight but weaning weight and carcass quality at 5 months of age were not different between groups (Wilson *et al.*, 2016). Thus, excess maternal nutrition and maternal obesity both affect lipid and glucose metabolism in offspring and may also alter body composition and muscle quality.

Undernutrition

As for excess nutrition, maternal undernutrition has been extensively studied in the ewe (Table 2). Only severe maternal undernutrition reduces birthweight whereas moderate undernutrition appears un-noticed in terms of offspring birthweight (Bispham *et al.*, 2003; Gardner *et al.*, 2005; Ford *et al.*, 2007; Hoffman *et al.*, 2014, 2016; Field *et al.*, 2015; Kleemann *et al.*, 2015; Sen *et al.*, 2016; Whorwood *et al.*, 2016). Nevertheless, lambs born to undernourished ewes have reduced plasma IGF1 and T3 (triiodothyronin) concentrations (Hoffman *et al.*, 2014; Field *et al.*, 2015) and physiological pathways involving corticosteroid hormones are disturbed (Whorwood *et al.*, 2016). Maternal undernutrition has also been associated with alterations in glucose metabolism, including hyperglycemia or hyperinsulinemia, increased insulin secretion by β -cells and reduced glucose tolerance (Gardner *et al.*, 2005; Ford *et al.*, 2007; Hoffman *et al.*, 2016). Intra-muscular lipid depositions are also increased in these lambs together with modifications in muscular fiber development (Ford *et al.*, 2007; Reed *et al.*, 2014) and increased perirenal fat mass was observed with or without reduction of subcutaneous fat (Gardner *et al.*, 2005; Ford *et al.*, 2007; Hoffman *et al.*, 2014, 2016).

In goats, a progressive maternal undernutrition (goats were fed 50 to 80% of the spontaneous intake of controls) in the last third of gestation reduced birthweight in male kids only although Non-esterified fatty Acid concentrations (NEFA) were increased in all kids (Laporte-Broux *et al.*, 2011). Subsequently at 1 and 2 years of age, restricted female offspring ate more than controls but no difference in energy metabolism was evidenced between groups (Laporte-Broux *et al.*, 2012).

In beef cattle, feeding cows at 80% requirements between 3 and 6 months of gestation reduced subcutaneous rib fat thickness and increased the intra- to inter-muscular fat ratio in 7 months old calves (Mohrhauser *et al.*, 2015). The birthweight of calves born to Angus cross-bred cows fed 60% of their requirements between 30 and 85 days or between 30 and 140 days of gestation was the same as offspring

born to cows fed 100% of requirements but their liver was heavier (Prezotto *et al.*, 2016). Moreover, nutritional supplementation of restricted beef heifers during pregnancy did not increase offspring birthweight nor subsequent performance (Summers *et al.*, 2015) but increased feedlot efficiency and altered carcass characteristics with a tendency for high fat concentrations in the meat of animal born to restricted, non-supplemented heifers (Summers *et al.*, 2015).

In rabbits, a 50% maternal undernutrition from 7 to 19 days or from 20 to 27 days of gestation (31 days pregnancy) reduced pups' birthweight but post-natal growth, feeding behavior and body composition were not altered until 2,5 months of age (Lopez-Tello *et al.*, 2017).

Thus, whatever the species, although maternal undernutrition may not alter birthweight, offspring lipid and glucose metabolism are usually disturbed, affecting body composition and muscular development.

Effect of maternal metabolism

Independently from nutrition, maternal metabolism can be affected by many factors. Insulinoreistance is usually linked to obesity but can also be associated to production. Indeed, high yielding dairy cattle are prone to insulinoreistance because of their high energy requirements for milk production inducing a negative energy balance and this lactational insulinoreistance can persist for subsequent pregnancies (Bossaert *et al.*, 2008; De Koster and Opsomer, 2013; Zachut *et al.*, 2013; Opsomer *et al.*, 2017). Dairy cows insulinoreistant in late gestation produce lighter calves with reduced IGF1 plasma concentrations and increased insulinemia at birth (Kawashima *et al.*, 2016). Effects on subsequent offspring production have not been studied but epidemiological data indicate a slightly reduced milk yield if offspring from dams inseminated at peak lactation (González-Recio *et al.*, 2012).

Effect of maternal parity

The study of maternal age and parity on offspring development is difficult in production animals as age and parity are usually linked. Heifers are also non-lactating at breeding in contrast to cows.

In the horse, primiparous mares produce smaller and lighter foals at birth than multiparous mares (Fig. 2; Doreau *et al.*, 1991; Lawrence *et al.*, 1992; Pool-Anderson *et al.*, 1994; Cymbaluk and Laarveld, 1996; Wilsher and Allen, 2003; Elliott *et al.*, 2009; Klewitz *et al.*, 2015; Vazquez *et al.*, 2015; Meirelles *et al.*, 2017). Moreover, it has been shown that foals born to primiparous mares remain smaller until 1 year of age and lighter until 4 months of age compared with foals born to multiparous mares (Pool-Anderson *et al.*, 1994; Cymbaluk and Laarveld, 1996; Zoch *et al.*, 2016; Meirelles *et al.*, 2017). This difference of growth seems to be linked with decreased IGF-1 serum concentration in primiparous foals (Cymbaluk and Laarveld, 1996).



Table 2. Summary of studies performed on the effects of undernutrition in pregnant ewes on the post-natal development of the offspring. The level of undernutrition is expressed as a percentage of the energy content ingested by the control group.

Undernutrition	Undernutrition period	Function	Age	Phenotype	Source
Periconceptual undernutrition					
70%	From 17 days before insemination to 6 days after	Growth	Birth 5 days	= Live weight ↗ Liver weight	Kleeman <i>et al.</i> , 2015
Undernutrition in early gestation					
50%	28 to 79 days of gestation	Growth	135 days of gestation	= Live weight	Field <i>et al.</i> , 2015
		Growth	Birth From 4 to 8 months	↘ Live weight ↗ Live weight	
50%	28 to 78 days of gestation	Body condition	8 months	↗ Perirenal and muscle adipose tissue	Ford <i>et al.</i> , 2007
		Carbohydrate metabolism	2 months 8 months	↗ Basal glycaemia ↗ Pancreatic β cell response ↘ Pancreatic β cell response	
		Growth		= live weight, ↗ total length, ↗ kidneys weight	
50%	28 to 77 days of gestation	Gene expression	Birth	↗ <i>Glucocorticoid receptor</i> expression (adrenal, liver, lung, perirenal adipose tissue, kidneys) ↘ <i>11-βHSD2</i> expression (adrenals, kidneys)	Whorwood <i>et al.</i> , 2016
40%	28 to 80 days of gestation	Growth	Birth	↗ Live weight	Bispham <i>et al.</i> , 2003
50%	30 to 80 days of gestation	Growth	Birth 5 months	= Live weight ↘ Live weight	Sen <i>et al.</i> , 2016



Undernutrition	Undernutrition period	Function	Age	Phenotype	Source
Undernutrition in late gestation					
60%	From 116 days of gestation	Growth	1 day 3 months	↘ Live weight, ↘ thoracic perimeter ↘ Back subcutaneous adipose tissue thickness	Hoffman <i>et al.</i> , 2014
		Endocrinology	1 day From 1 day to 3 months	↘ T3 concentration ↘ IGF1 concentration ↘ IGFBP3 concentration	
50%	From 110 days of gestation	Growth	From birth to 1 year	= Live weight	Gardner <i>et al.</i> , 2005
		Carbohydrate metabolism	1 year	↘ Glucose tolerance ↘ GLUT4 expression in the perirenal adipose tissue	
50%	From 105 days of gestation	Body condition	1 year	↗ Fat mass	Khanal <i>et al.</i> , 2014
		Growth	From birth to 6 months 6 months	↘ Live weight ↘ Subcutaneous adipose tissue / visceral adipose tissue ratio	
Undernutrition throughout gestation					
50%	From 28 days of gestation	Growth		= Live weight, ↗ liver weight	Field <i>et al.</i> , 2015
		Carbohydrate metabolism	135 days of gestation	↗ Umbilical insulinemia	
60%	From 31 days of gestation	Endocrinology		↗ Umbilical IGF1 concentration	Reed <i>et al.</i> , 2014 Hoffman <i>et al.</i> , 2016
		Growth	From 1 day to 3 months 3 months	= Live weight, total length ↗ Heart weight	
		Body condition	3 months	↘ Back subcutaneous adipose tissue thickness	
		Carbohydrate metabolism	3 months	↗ Basal insulinemia ↗ Basal insulin/glucose ratio	
		Muscle function	1 day 3 months From 1 day to 3 months	↗ Fibres area (cross section) ↘ Fibres area (cross section) ↗ Lipid accumulation in muscle	

11-βHSD: 11β-hydroxysteroid dehydrogenase : converts cortison into cortisone; T3: Triiodothyronine; IGF1: Insulin Growth Factor 1; IGFBP3: Insulin growth Factor Binding Protein 3; GLUT4: Glucose transporter 4.



In dairy cattle, heifers have a shorter gestation length and produce smaller (-9%) and lighter calves compared to cows (Kertz *et al.*, 1997; Kamal *et al.*, 2014, 2015) with a reduced body mass index (weight/withers' height * crown-rump length) at birth (Kamal *et al.*, 2014, 2015). Nevertheless, alterations of the glucose

metabolism were not observed at birth in these calves (Kamal *et al.*, 2015). Finally, heifers' colostrum contains less calcium, phosphorus and magnesium than multiparous cow colostrum, indicating that colostrum quality is altered, maybe for other components (Kume and Tanabe, 1993).

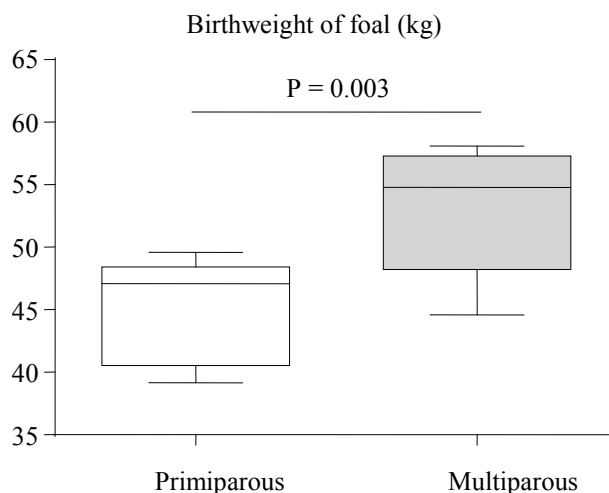


Figure 2. Birthweight of foals depending on the parity of the mare. Data derived from Doreau *et al.* (1991); Lawrence *et al.* (1992); Wilsher and Allen (2003); Elliott *et al.* (2009); Meirelles *et al.* (2017).

Practical implications for embryo transfer

The data presented above show clear evidence that maternal size and nutrition may influence offspring size but also metabolism and production. Other production and health traits, such as immunity, feeding behavior but also fertility may also be affected (Chadio and Kotsampasi, 2014; Chavatte-Palmer *et al.* 2014). This pleads for a very careful choice of embryo recipients in terms of breed and size but also underlines the importance of the management of these animals before and during pregnancy. The molecular basis for these effects is epigenetic mechanisms (Gonzalez-Recio *et al.*, 2015; Triantaphyllopoulos *et al.*, 2016). Future research is needed to explore if epigenetic markers could be used as predictors of long term outcomes in offspring.

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