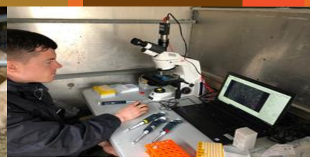
Bull development and its impact on sexual maturation and sperm production



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Overview

- **Background**
  - Why advance sexual development in the bull calf?
  - Post-natal sexual development of bull calf
- **Early life nutritional management on:**
  - Endocrine and molecular response of HPT axis
  - Age at onset of puberty and sexual maturation
  - Post pubertal semen characteristics
  - Sperm methylome
  - Fertility
- **Nutritional supplements and bull fertility**



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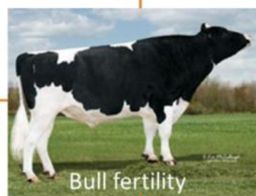
Factors Affecting Bull Fertility

Genetics

Epigenetics



Environmental

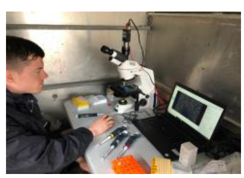
Systems Physiology and Biology

Parisi et al. (2014) Mississippi State University

Sexual development in the bull - definitions

Puberty: An ejaculate containing ≥ 50 million sperm with ≥ 10% progressive linear motility (Wolf *et al*., 1965)

Sexual maturation: ejaculate with > 30% progressive motility, > 70% morphologically normal sperm (Brito *et al*., 2004)



Effect of breed on age at puberty

Table 1.—Pubertal characteristics of various breeds of beef bulls[1]

Pubertal trait	Hereford	Angus	H x A crossbred	A x H crossbred	Red Poll	Brown Swiss	All bulls[2]
	Breed group						
Number of bulls evaluated	5	5	6	5	5	5	31
Age in days at:							
First sperm	266	265	258	268	252	236	258 ± 2
50 million sperm[3]	326	295	300	296	283	264	294 ± 4
First completed mating	371	354	366	341	333	250	336 ± 5
Body weight in pounds at:							
First sperm	491	543	535	535	513	598	535 ± 9
50 million sperm[3]	574	601	614	581	568	649	601 ± 9
First completed mating	625	708	730	669	645	623	671 ±13
Scrotal circumference (inches) at:							
First sperm	9.4	10.8	9.8	10.5	10.1	10.3	10.2 ± .2
50 million sperm[3]	11.0	11.3	10.9	11.2	10.8	10.9	11.0 ± .1
First completed mating	11.5	12.2	12.0	12.0	11.6	10.7	11.7 ± .1

[1]Least-squares means.
[2]Data given as mean ± SEM.
[3]Based on first production of an ejaculate containing at least 50 million sperm with a minimum of 10 percent motility.

Lunstra (1982)

Effect of Age on Puberty and Sexual Maturity in Bulls

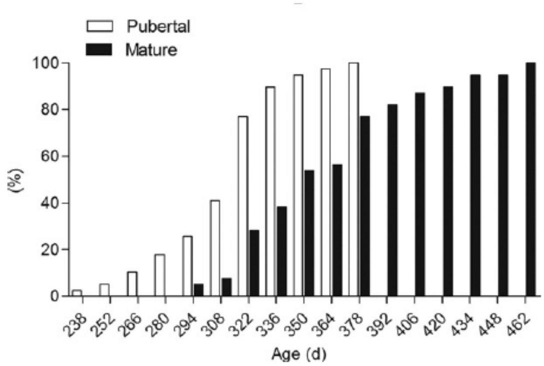
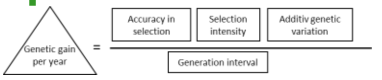


Fig. 3. (A) Mean sperm viability and morphology according to age in 39 Angus × Charolais and Angus bulls. (B) Proportion of pubertal (ejaculate containing ≥ 50 × 10^6 sperm with ≥10% motile sperm) and mature (ejaculate containing ≥30% motile and ≥70% morphologically normal sperm) bulls according to age.

Brito et al. (2007b)

Why advance sexual development?

- **Generation interval limits genetic gain**



  - Generation interval = average age of the parents when offspring are born
- **Genomic selection**
- **Puberty and sexual maturation**
- **Semen production from peri-pubertal bulls**
  - Lower semen quantity and quality from peri-pubertal bulls (Murphy *et al*., 2018)
  - 30-50% of semen yield of mature bull in first year at stud (Amann and DeJarnette, 2012)
  - Maximum daily sperm production/gram testis ~20 weeks post-puberty (Almquist, 1982)

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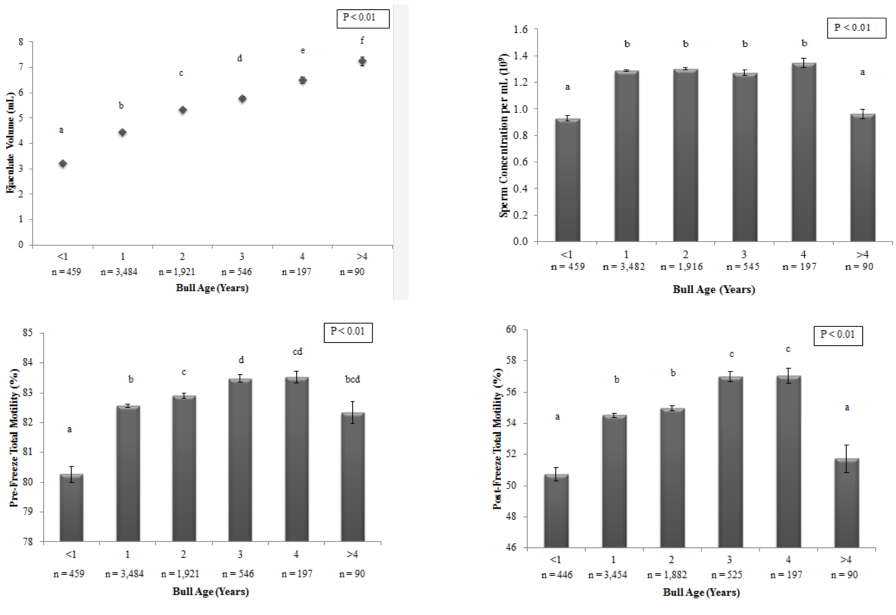
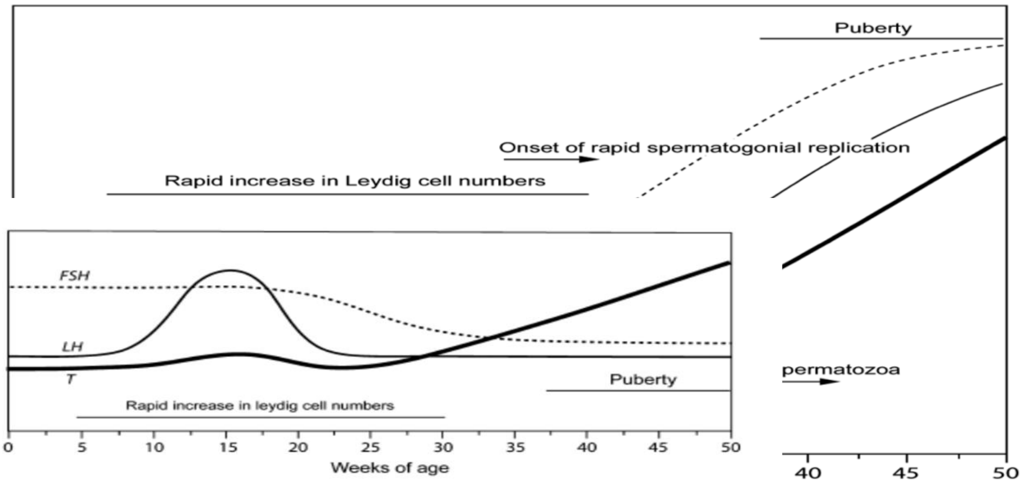
Effect of Bull Age on Semen Parameters



Murphy et al. (2018)

Post-natal sexual maturation of the bull



Timing of the early LH rise will affect the age at puberty

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Rawlings *et al.* (2008)

Table 1 *Effects of plane of nutrition on pubertal and sexual development in bulls*

	Breed	Start age (days)	Diets			*n*	ADG (kg/day)	Age at puberty (days)[1]	Age at maturity (days)[2]	Paired testes weight (g)	Experiment end age (days)
Brito *et al.* (2007b)	Angus and Angus × Charolais	56	Pre 26 weeks of age Control: 13.2% CP, *ad libitum* Restricted: 75% of control consumption		Post 26 weeks of age Control/control: *ad libitum* Restricted/control Restricted/high: 14.4% CP	24	–	293^{a} 331^{b} 313^{ab}	–	600^{a} 528^{b} 553^{ab}	490
Brito *et al.* (2007c)	Angus and Angus × Charolais	70	Pre 30 weeks Control: 13.5% CP High: 15.1% CP until 19 weeks of age, 21.3% CP thereafter		Post 30 weeks All received control	33	–	327 314	–	531^{a} 611^{b}	518
Brito *et al.* (2007d)	Angus and Angus × Charolais	70	Low: 12.3% CP Medium: 13.1% to 16.3% CP, diet changed after 30 weeks of age High: 20.4% CP			23	–	321^{a} 299^{b} 288^{b}	–	520^{a} 549^{a} 655^{b}	490
Bollwein *et al.* (2016)	Holstein-Friesian	2	Pre 5 weeks of age Restricted: 4 l MR *Ad libitum*-low: <6 l MR *Ad libitum*-high: >12 l MR	Post 5 weeks of age All received a conventional finishing ration		24	0.38^{a} 1.28^{b}	275 274 278	–	–	~448
Byrne *et al.* (2017)	Holstein-Friesian and Jersey	21	Pre 10 weeks of age Low HF: 4 l MR, JE: 3.5 l MR, all 1 kg concentrate High HF: 8 l MR, JE: 6 l MR, all *ab libitum* concentrate	8 to 16 weeks of age Low HF: 1.7 kg, JE 1.4 kg concentrate High: *ad libitum*	Post 16 week of age Low: 0.5 kg concentrate High: *ad libitum* concentrate	34	0.99^{a} 0.76^{b} 0.63^{c} 0.44^{d}	[3]HHF: 37^{a} HJE: 34^{a} LHF: 43^{b} LJE: -	–	–	343
Byrne *et al.* (unpublished)	Holstein-Friesian	14	Pre 10 weeks of age as HF above	10 to 24 weeks of age Low: 1 kg concentrate High: *ad libitum* concentrate	Post 24 weeks of age Low/low: 0.5 kg concentrate High/low: 0.5 kg concentrate Low/high: *ad libitum* concentrate High/high: *ad libitum* concentrate	83	0.57^{a} 0.84^{b} 0.96^{b} 1.24^{c}	319^{a} 283^{b} 323^{a} 298^{b}	343^{a} 314^{b} 352^{a} 331^{b}	626^{a} 658^{b} 594^{a} 660^{b}	504
Dance *et al.* (2015)	Holstein-Friesian	3	Pre 31 weeks of age Low: 12.2% CP Medium: 17.0% CP High: 20% CP		Post 31 weeks of age All received medium	26	–	369^{a} 327^{ab} 324^{b}	[4]385 391 366	562^{a} 611^{ab} 727^{b}	504
Harstine *et al.* (2015)	Holstein-Friesian	58	Pre 32 weeks of age Control: 0.92 Mcal/kg High: 1.24 Mcal/kg Diets were isonitrogenous (18.2% CP)		Post 32 weeks of age All received control	15	1.00^{a} 1.51^{b}	302 323	–	268^{a} 318^{b}	569

[a,b,c,d]Values within study with different superscripts differ significantly ($P<0.05$).
[1]Based on ability to produce an ejaculate containing ⩾50 million sperm with ⩾10% progressive linear motility (Wolf *et al.*, 1965).
[2]Based on ability to produce a pubertal ejaculate with ⩾70% morphologically normal sperm and ⩾30% progressive linear motility (Brito *et al.*, 2004).
[3]Based on attainment of scrotal circumference of 28 cm (Lunstra *et al.*, 1978).
[4]Taken from Dance *et al.* (2016).

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Kenny and Byrne (2018). *Animal. 12 (S1):36-44*

Objective

Effect of plane of nutrition (i) pre- and (ii) post-six months of age in Holstein-Friesian bulls, on age at puberty and post-pubertal semen production

Byrne *et al.* (2018). *J. Dairy Sci.* 101(4):3447-3459
Byrne *et al*. (2018). *J. Dairy Sci.* 101(4):3460-3475

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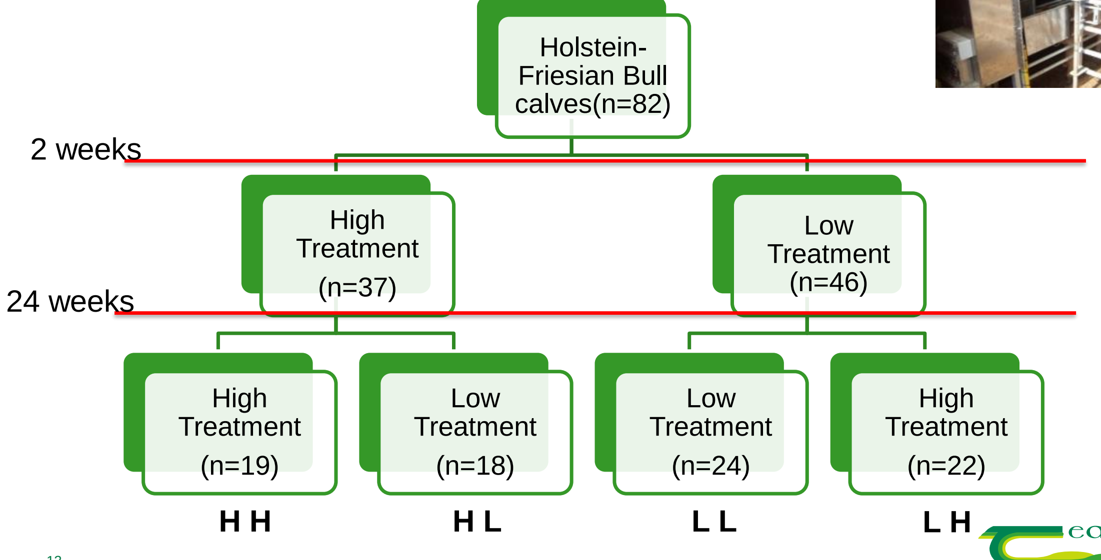
Experimental design



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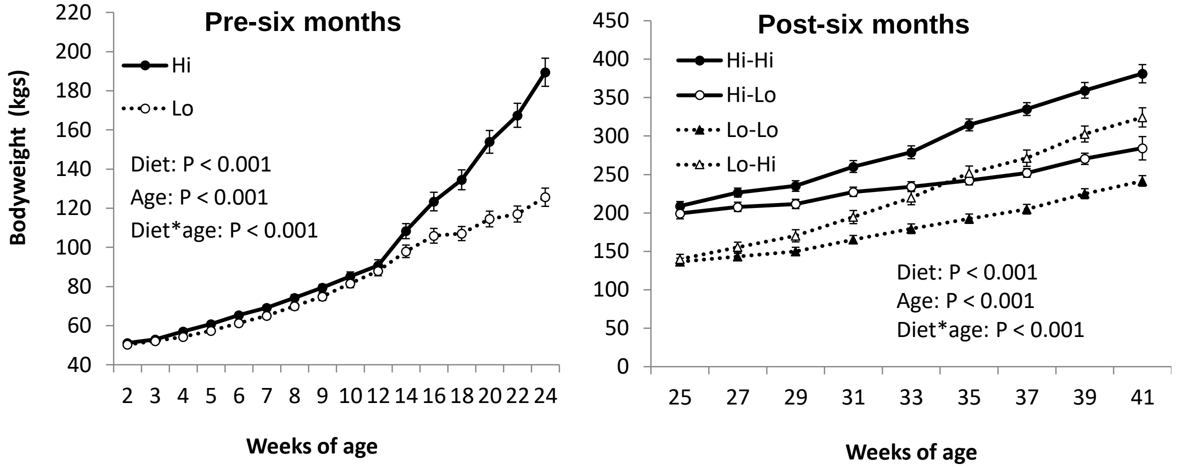
Byrne *et al.* (2018). *J. Dairy Sci. 101(4):3447-3459*

Plane of nutrition offered pre or post-six months of age on body weight



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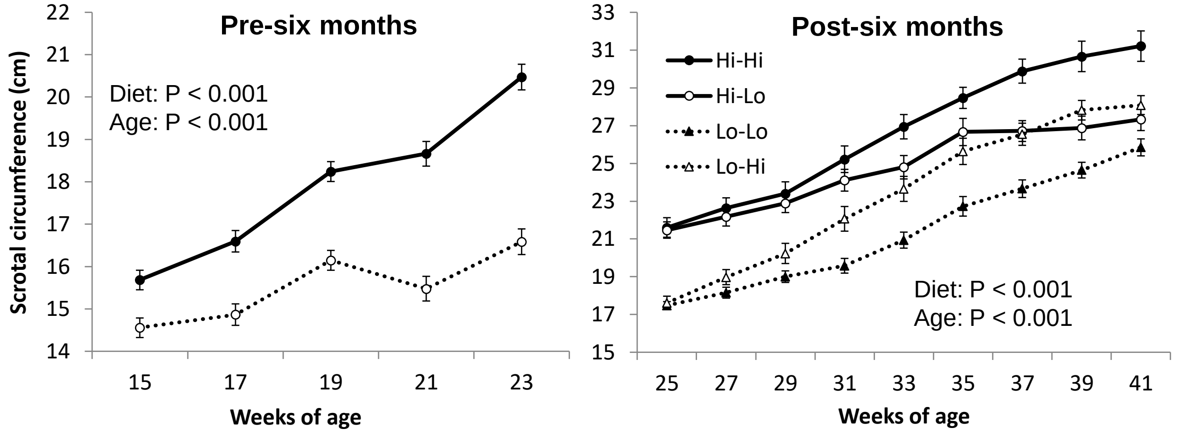
Byrne *et al.* (2018). *J. Dairy Sci. 101(4):3447-3459*

Plane of nutrition offered pre or post-six months of age on scrotal circumference



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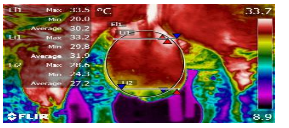
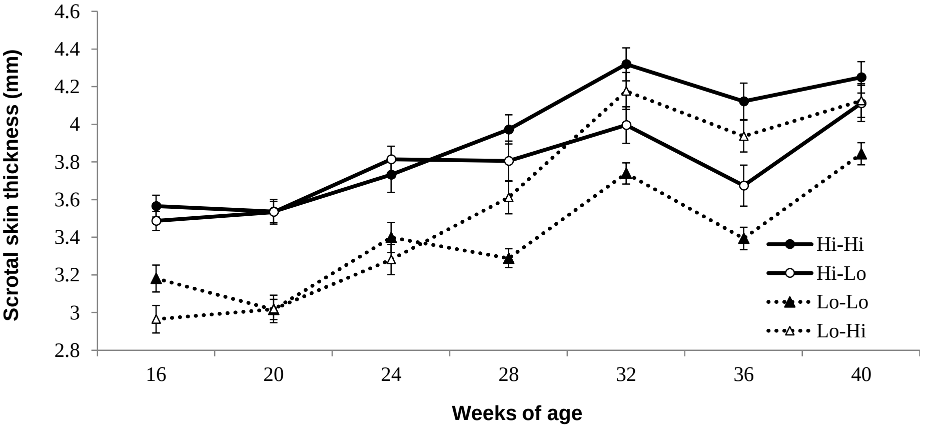
Byrne *et al.* (2018). *J. Dairy Sci. 101(4):3447-3459*

Scrotal temperature



- Temperature of the testes must be 2-6ºC lower than core body temperature
- Increased testicular temperature, irrespective of the cause, reduces semen quality and can cause of infertility in bulls
- Duration of the decrease in semen quality related to severity and duration, with sperm morphology.
- At least 6 weeks to recover normal spermatogenesis
- Resumption of normal fertility may take longer
- Increased scrotal temperatures may be a consequence of:
  - ➢contraction of disease
  - ➢injury
  - ➢increase in fatness of scrotum

Scrotal Skin Thickness



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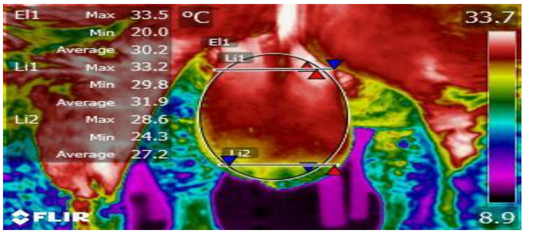
Byrne *et al.* (2018). *J. Dairy Sci. 101(4):3447-3459*

Scrotal surface temperature (28 to 36 wk of age)

	Plane of nutrition (PON)				Month			Significance[1]		
	High/High	High/Low	Low/High	Low/Low	May	June	July	PON	Month	PON*Month
Gradient	5.6[a] (0.14)	4.5[b] (0.15)	5.8[a] (0.16)	4.7[b] (0.14)	4.9[a] (0.15)	5.2[ab] (0.13)	5.4[b] (0.14)	***	**	NS
Average overall	32.8[ab] (0.13)	33.1[a] (0.16)	32.7[b] (0.15)	33.0[a] (0.16)	32.9[a] (0.01)	33.9[b] (0.10)	32.0[c] (0.09)	*	***	NS

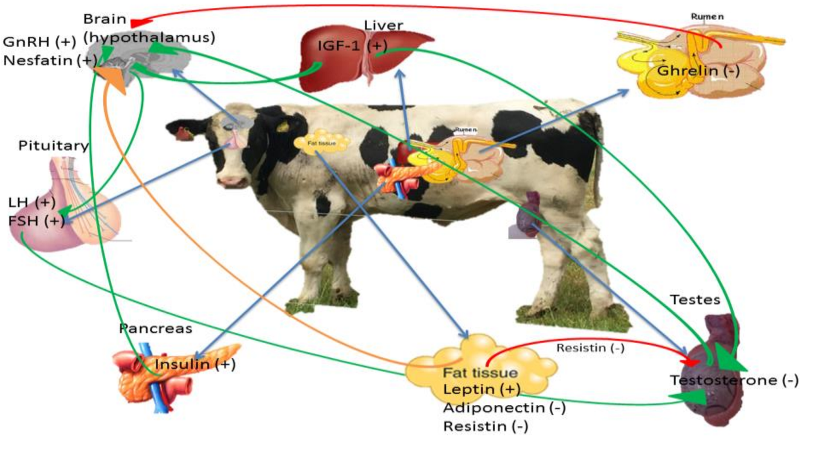
(S.E.M)

[1]*=P<0.05, **= P<0.01, ***P<0.001.
[a,b] = superscripts with same letter are not different (P>0.05).



Byrne *et al.* (2018). *J. Dairy Sci. 101(4):3447-3459*

Metabolic hormones and hypothalamic-pituitary-testicular function



Kenny *et al.* (2018) *Reprod. Fertil. Dev.* 30: 101–117

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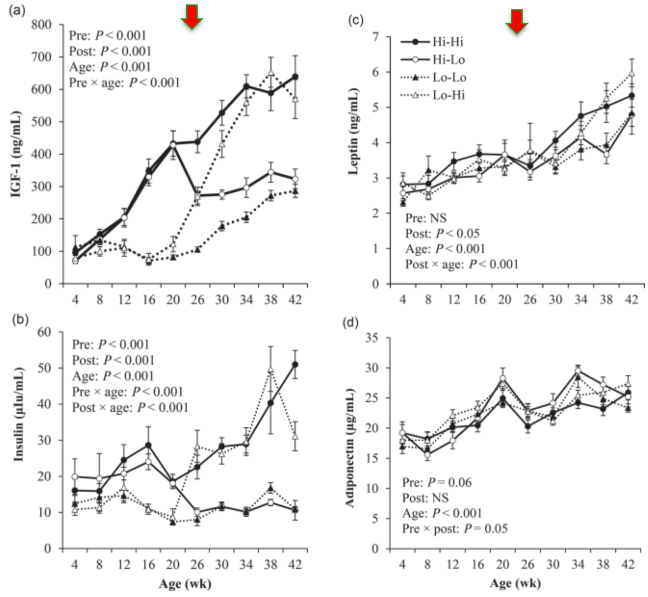
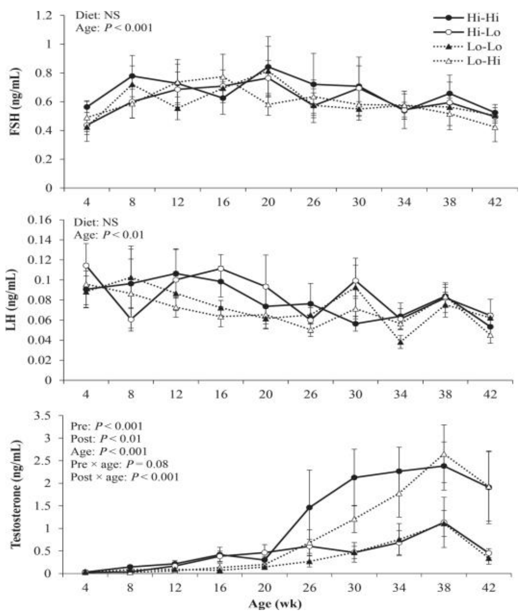
Metabolic hormones

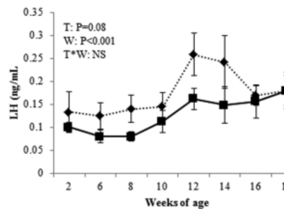


24 weeks of age

Byrne et al. (2018b)

Reproductive hormones





English et al. (2018)

Byrne *et al*. (2018b)

Sexual development

Table 4. Effect of high (Hi) or low (Lo) plane of nutrition during the pre- or post-6 mo period on puberty and reproductive characteristics in Holstein-Friesian bulls (mean ± SEM)

Variable[1]	Plane of nutrition (pre-post) Hi-Hi (n = 19)	Hi-Lo (n = 18)	Lo-Lo (n = 22)	Lo-Hi (n = 24)	Significance Pre	Post	Pre × Post
Age at puberty[2] (d)	298 ± 6.3[a]	283 ± 5.6[a]	319 ± 3.9[b]	323 ± 6.5[b]	***	NS	0.09
Weight at puberty (kg)	404 ± 11.8[a]	287 ± 6.52[b]	269 ± 5.52[b]	374 ± 15.0[a]	NS	***	NS
SC at puberty (cm)	31 ± 0.52[a]	29 ± 0.34[ab]	28 ± 0.39[b]	29 ± 0.74[ab]	*	0.06	NS
Age at sexual maturation[3] (d)	331.3 ± 7.10	314.2 ± 7.48	343.2 ± 7.13	352.3 ± 3.65	***	NS	NS
Days from puberty to maturity	29.9 ± 1.62	30.9 ± 2.04	32.6 ± 2.10	29.4 ± 0.56	NS	NS	NS
Paired testis weight at 72 wk of age (g)	660.4 ± 28.53	658.5 ± 19.75	626.9 ± 19.97	594.2 ± 26.59	*	NS	NS
Paired epididymal weight at 72 wk of age (g)	59.6 ± 2.57	61.2 ± 1.57	55.1 ± 2.78	57.9 ± 1.67	NS	NS	NS
Sertoli volume density (%)	1.09 ± 0.28	1.25 ± 0.31	1.06 ± 0.27	1.02 ± 0.46	NS	NS	NS
PS volume density (%)	2.39 ± 1.01	2.49 ± 0.71	2.51 ± 0.68	2.51 ± 0.89	NS	NS	NS
RS volume density (%)	2.24 ± 0.95	1.99 ± 1.07	1.99 ± 0.71	1.98 ± 0.63	NS	NS	NS

[a,b]Values within row with different superscripts differ significantly.

[1]SC = scrotal circumference; PS = pachytene spermatocytes; RS = round spermatids.

[2]Ability to produce an ejaculate containing ≥50 × 10^6 spermatozoa and ≥10% progressive linear motility (Wolf et al., 1965).

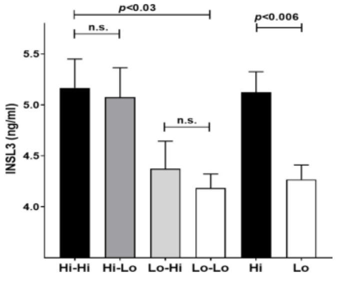
[3]Ability to produce an ejaculate containing ≥70% morphologically normal spermatozoa and ≥30% progressive linear motility (Brito et al., 2004).

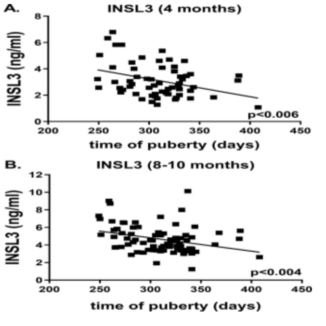
*$P < 0.05$, ***$P < 0.001$.

Byrne *et al.* (2018). *J. Dairy Sci. 101(4):3447-3459*

INSL3 - stable marker of puberty?

Insulin-like peptide 3 (INSL3) - peptide hormone biomarker uniquely reflecting Leydig cell functional capacity

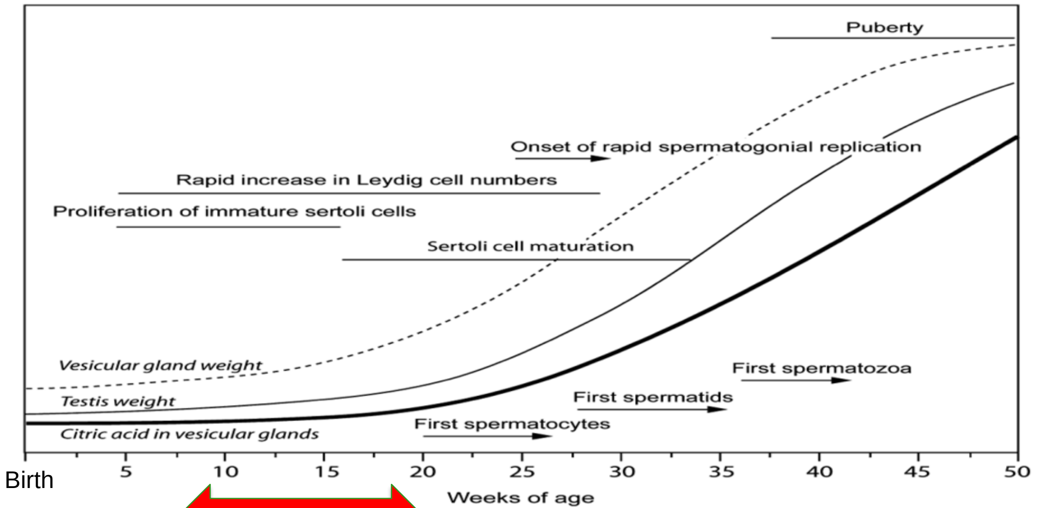




- Early life nutrition apparently a key promoter of the development of Leydig cell functional capacity and involved in the dynamic progression of puberty.
- INSL3 also upregulated in the testicular transcriptome of calves on a high plane of nutrition at 12 and at 18 weeks of age

Anand-Ivell et al. (2019)

Post-natal sexual maturation of the bull



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Rawlings *et al.* (2008)

Objective: to study the effect of early life nutrition and the morphological and molecular characteristics of the HPT axis of Holstein-Friesian bull calves at 12 and at 18 weeks of age

- Arcuate region of hypothalamus
- Anterior pituitary
- Testes
- Adipose tissue

Analyses

- RT-PCR
- miRNASeq
- RNASeq
- Proteomics
- Histology, IHC

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English et al. (2018a,b,c); Coen et al. (unpubl.)

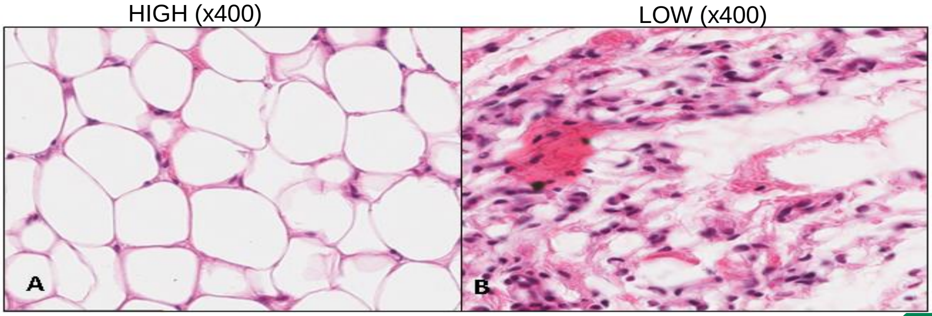
Adipocyte Morphology

Effects of a high or low plane of nutrition on adipocyte cell number and diameter at 18 weeks of age in Holstein-Friesian bull calves (mean ± sem).

	High	Low	Significance
Cell Number (per 1.25 mm^{2})	291 ± 47.2	7.5 ± 4.0	***
Cell Diameter (µm)	36.9 ± 2.89	3.7 ± 1.94	***

*** = P<0.001,

HIGH (x400) LOW (x400)



P<0.001

31 English (2018). *BMC Genomics* 19(1):281.

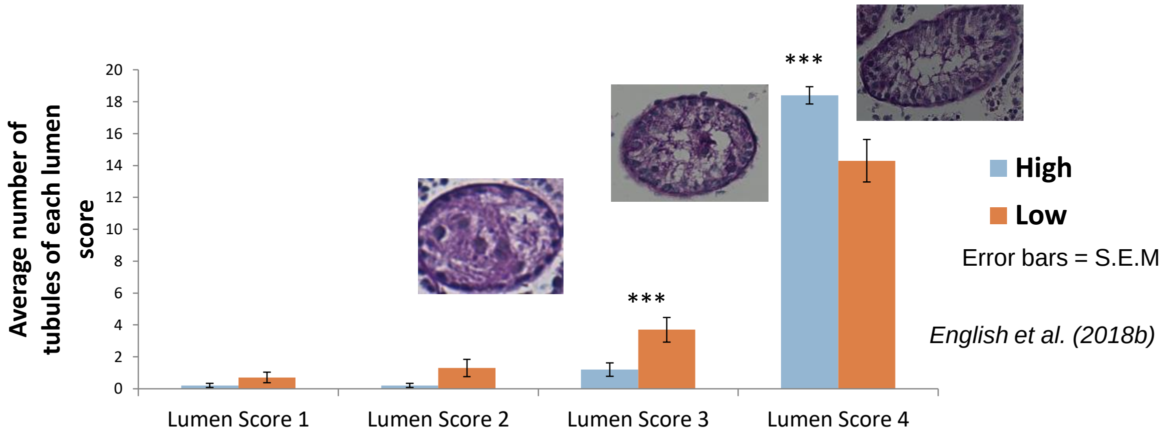
Testis weight and morphological properties in Holstein-Friesian bull calves (18 wks old)

	Low	**High**	**SEM**	**Significance**
Paired testes weight (g)	31.4	55.4	2.91	***
Seminiferous Tubule Diameter (µm)	72.5	85.4	1.76	***
% Gonocyte and Prespermatogonia	57	31.5	1.66	***
% Spermatogonia	43	68.5	1.66	***
No. of Sertoli cells	24	28	0.65	*
Nuclear vol. density of Sertoli cells[1]	8.4	9.4	0.35	***

[1]Johnson & Nguyen (1986)

32 English *et al.* (2018) unpubl.

Plane of nutrition and seminiferous tubule lumen development



	Immature			Mature	
Lumen score	1	2	3	4	5

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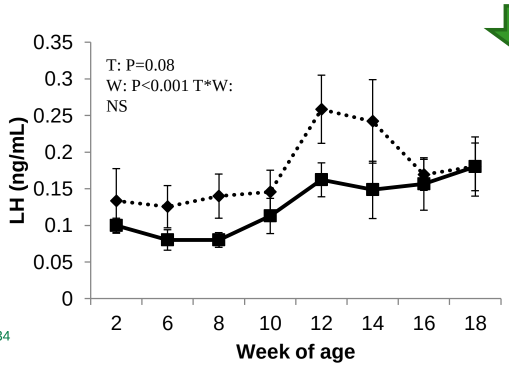
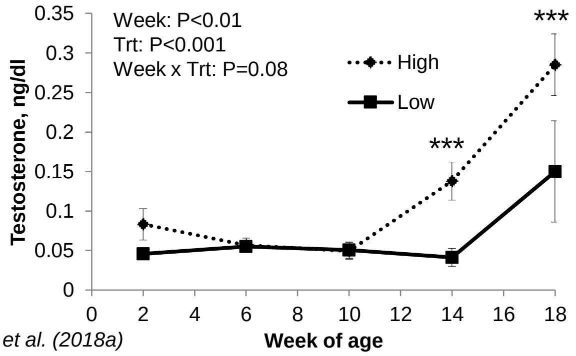
RNAseq Analysis of Testes (18 wks of age)

- 1,346 DEG between H and L calves
- A high plane of nutrition increased the expression of genes affecting processes including androgen and cholesterol biosynthesis
  - Super pathway of cholesterol biosynthesis ($P<0.0001$)
  - Androgen biosynthesis ($P<0.0001$)

English *et al*., 2018.



English et al. (2018a)



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Molecular Regulators of Puberty

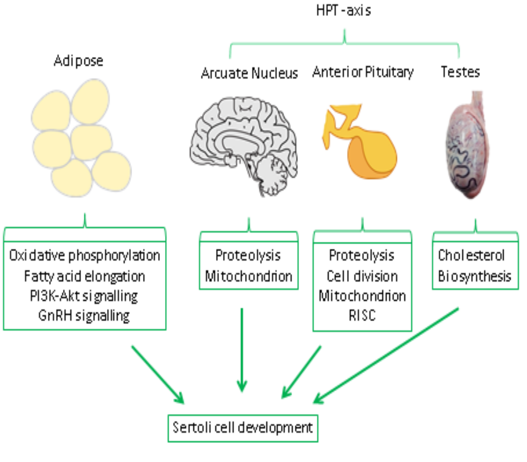
RNAseq analysis of HPT –axis

- At 12 weeks of age 83, 37 and 20 DEG in ARC, AP and testes, respectively
- Limited number of DEG within ARC and pituitary at 18 weeks of age
- >1300 DEGs in testes *English et al. (2018a)*

Gene co-expression analysis

- Interactions between genes governing a phenotype
- Weighed Gene Co-expression Network Analysis (WGCNA) (Langfelder and Horvath, 2008)
  - Performed individually on RNAseq datasets from each tissue of the HPT-axis as well as adipose tissue
  - 12k to 14k genes across each of four tissues
  - Networks of genes were correlated with testicular abundance of Sertoli cells

Weighted Gene Co-expression Network Analysis



Genetic variants associated with sexual maturation in the bull calf

PENK
- Opioid system, influencing the HPG axis
- SNPs identified in bulls and heifers (Canovas et al., 2014; Dias et al., 2017)

SCG2, SCG3
- Neuroendocrine secretory proteins
- SNPs associated with puberty (Dias et al., 2017)

PROP1
- Development of the pituitary gland
- Production of LH, FSH and GH
- Key transcription factor involved in the regulation of puberty (Canovas et al., 2014)

Kenny et al. (2018)

Effect of nutritional management of the replacement heifer calf and subsequent reproductive development of male progeny

- AA heifer calves offered a high or low plane of nutrition from 4 to 8 months of age
- Age at puberty determined and bred at 16.5 months of age (same AI sire)
- Male foetuses recovered at 100 days of gestation
- H: n= 10 , L: n=12
- Measured crown-rump length and foetal weight
- Removed testes; one for immunohistochemistry, the other for RNA seq

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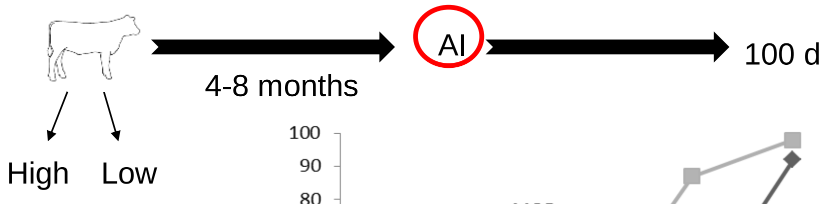

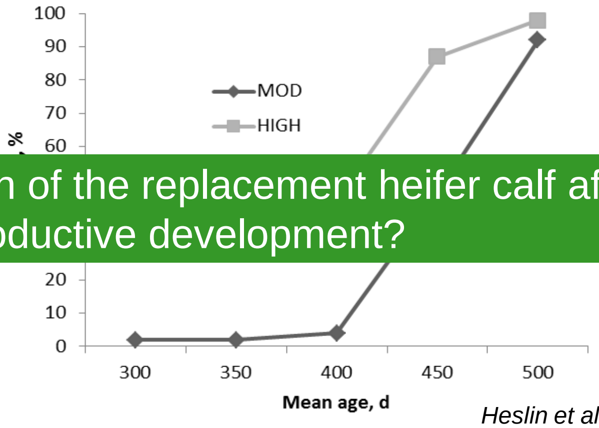

Could nutrition of the replacement heifer calf affect future progeny reproductive development?

Heslin et al. (2020), unpublished

A greater percentage of HI heifers were pubertal; at 300 d (2 vs. 32%), 350 d (2 v 41%), 400 d (4 v 44%) and 450 d of age (46 vs. 87%; *P* < 0.001).

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Preliminary Results

- Crown-rump length

H: 19.4cm ± 0.71 and L: 19.7cm ± 0.7

- Fetal weight

H: 309.5g ± 22.68 and L: 320.8g ± 31.95

O'Callaghan et al., unpublished

Preliminary Results

- Greater proportion of interstitial tissue in L fetuses (P<0.05).
- Greater seminiferous tubule density in H fetuses (P<0.05).

Preliminary testes gene expression results

Functions Annotation	***Molecules***
Development of reproductive system	*ADAMTS16, CLDN11, HNF1B, SFRP1, SLIT2, WFDC2, WNT4*
Development of genital organ	*ADAMTS16, CLDN11, HNF1B, SFRP1, WFDC2, WNT4*
Activation of gonadal cell lines	*CD14*
Differentiation of endometrial stromal cells	*WNT4*
Proliferation of gonadal cell lines	*HNF1B, RPRM*
Gonadogenesis	*ADAMTS16, CLDN11, SFRP1, WFDC2, WNT4*

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Early life nutrition and post-pubertal semen characteristics and fertility

- High plane of nutrition hastens onset of puberty and sexual maturity
- Latent effects on post-pubertal fertility??

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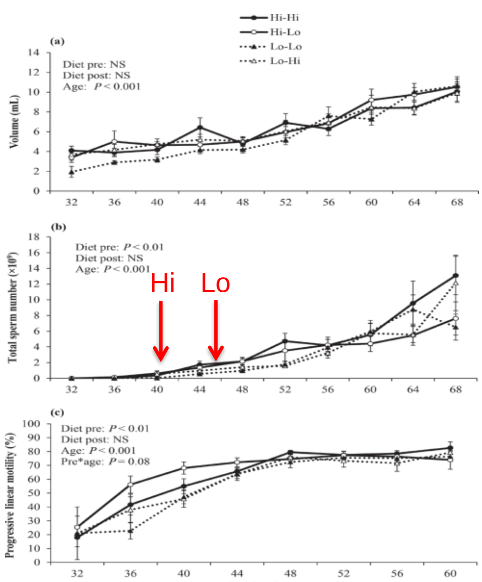
Post Pubertal Semen Traits (up to 17 months)



Byrne et al. (2018a)

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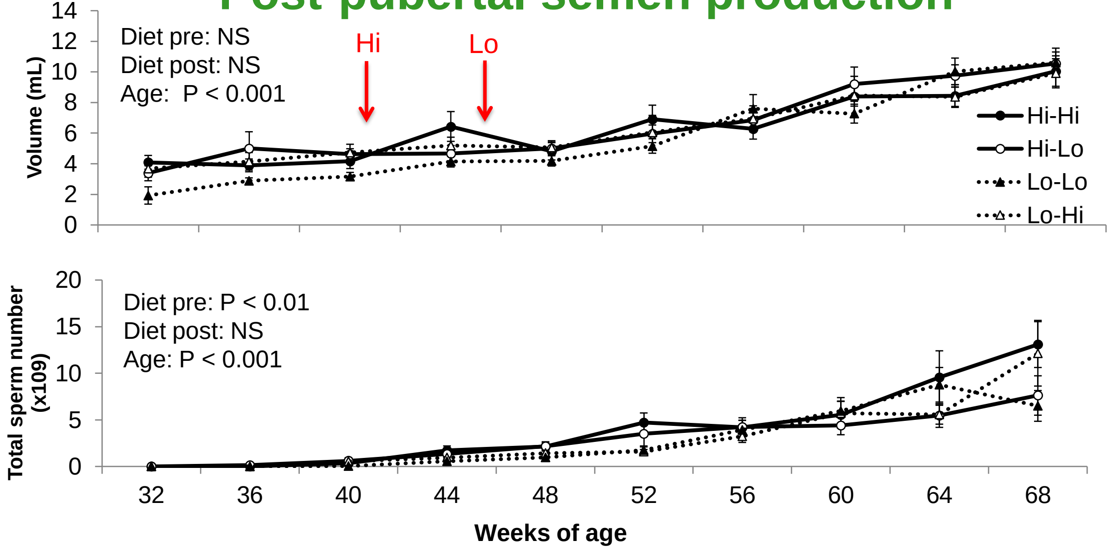
Post-pubertal semen production



Error bars= S.E.M.

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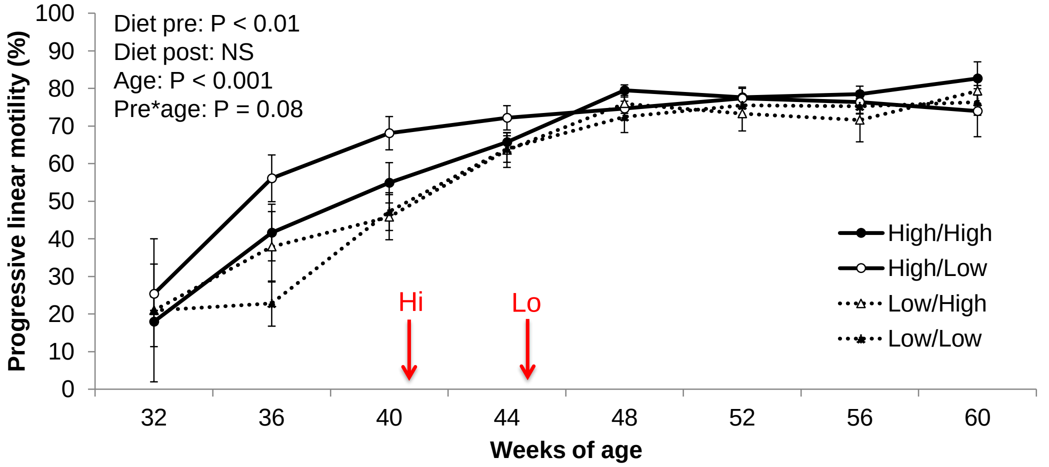
Byrne *et al.* (2018). *J. Dairy Sci. 101(4):3447-3459*

Sperm Motility



Error bars= S.E.M.

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Byrne *et al.* (2018). *J. Dairy Sci. 101(4):3447-3459*

Post pubertal semen production

Effect of early pre-pubertal plane of nutrition on estimated number[1] and sale value[2] of semen straws per ejaculate from HF bulls aged 12 -15 months

	High/High	High/Low	Low/High	Low/Low
Number of straws	308	205	177	92
Commercial value (€)	4619	3073	2662	1377

[1]15 million sperm/straw
[2]€15/straw

Byrne *et al.* (2018)

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Effect of calfhood nutrition on the sperm methylome

- Methylome is the set of nucleic acid methylation modifications in a cell
- Perturbations in the establishment of DNA methylation patterns during male germ cell differentiation have been associated with infertility in several species.
- **Objective:** to ascertain if early life plane of nutrition could have a latent effect on DNA methylation patterns in sperm produced post-puberty.
- **Methodology:** Sperm DNA methylation patterns from contrasted subgroups of bulls in the High (ejaculates recovered at 15 months of age; n= 9) and in the Low (15 and 16 months of age; n = 7 and 9, respectively) plane of nutrition bulls reported by Byrne *et al*. (2018) were obtained using Reduced Representation Bisulfite Sequencing (RRBS).
- Both 15 and 16 months were selected in the Low group as these bulls reached puberty approximately 1 month after the High bulls.

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Perrier et al., unpublished

Main results

- Hierarchical clustering demonstrated that sperm DNA methylation profile was predominantly a product of inter-animal variation rather than a function of either diet or age
- However, 580 differentially methylated CpGs (DMCs) were identified between the High and Low plane of nutrition groups
- Little to no effect of age (15 v 16 months old)
- DMCs were mostly hypermethylated in the High group, and enriched in endogenous retrotransposons, introns, intergenic regions, and shores and shelves of CpG islands.
- Comparison between High and Low groups showed that genes involved in spermatogenesis, Sertoli cell function, and the hypothalamic-pituitary-gonadal axis were targeted by differential methylation, reflecting the earlier timing of puberty onset in the High bulls
- An enhanced plane of nutrition in pre-pubertal calves, associated with advanced puberty, induced modest but persistent changes in sperm DNA methylation profiles after puberty

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Perrier et al. (2020)

Post pubertal fertility

Mean (± SEM) IVF cleavage and blastocyst rates for HF bulls at 64 weeks of age (n = 18) fed either a high or low plane of nutrition from 2 to 24 wk of age followed by a high or low plane of nutrition until attainment of puberty

Treatment	High/High	High/Low	Low/High	Low/Low
Oocytes (n)	924	1355	1345	1060
% Cleaved	75.0 ± 0.05	69.2 ± 0.04	75.5 ± 0.03	70.5 ± 0.05
% Blastocysts	28.6 ± 0.03	28.5 ± 0.03	31.8 ± 0.03	27.7 ± 0.02

Dance *et al.* (2016) also reported no difference in semen fertilizing ability or IVF blastocyst rate using a similar design

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Byrne *et al.* (2018)

Effect of dietary polyunsaturated fatty acids (PUFA) supplementation on semen volume and quality in young post-pubertal dairy bulls

Byrne *et al*. (2017).*Theriogenology* 90: 289-300

Dietary polyunsaturated fatty acids (PUFA)

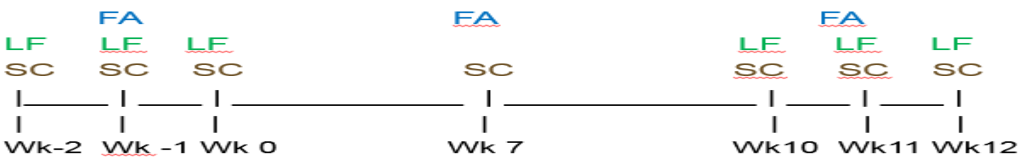
- **Sperm plasma membrane - high PUFA content**
- **Animals cannot synthesize n-3 and n-6 PUFA *de novo***
- **Some evidence for positive effects of PUFA supplementation on:**
  - sperm motility in boars (Rooke *et al*., 2001),
  - membrane fluidity in humans (Serinejad *et al*., 2010)
  - sperm number in rams *(Fair et al., 2014).*
- **Little consistency across studies/species**

Experimental design

- 50 post-pubertal dairy bulls (aged 13-15 months) assigned to one of three treatments

1. Control (n= 15)
2. n-6 safflower oil (n= 15)
3. n-3 PUFA enriched fish oil (n= 20)

- Partially rumen protected oil included at 2% of dietary DM



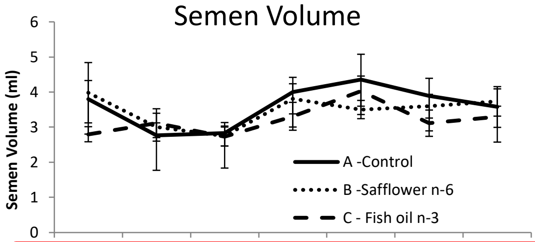
FA - semen fatty acid analysis

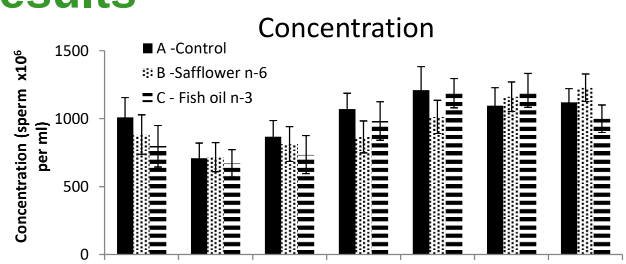
LF - live freeze

SC - semen collection

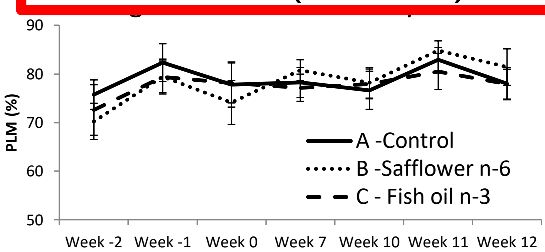
Byrne *et al*. (2017) *Theriogenology* 90:289-300

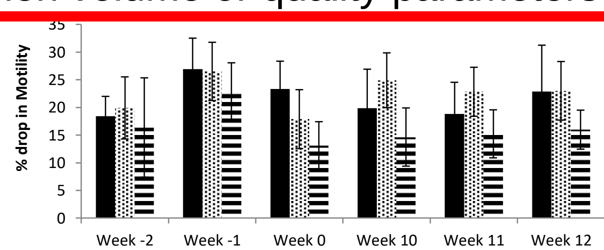
Results





No difference (P > 0.05) in semen volume or quality parameters





Byrne *et al*. (2017) *Theriogenology* 90:289-300

Error bars= S.E.M.

Overall summary

- Enhancing early calfhood nutrition leads to:
  - ✓ increased gonadotropin secretion
  - ✓ advanced steroidogenesis and testicular development
  - ✓ earlier onset of puberty and availability of saleable semen
- Mediated through complex interplay between metabolic signals and specialised neuropeptides within neuroendocrine centres of the brain and wider HPT axis
- Upregulation of molecular pathways more pronounced in hypothalamus & AP at 12 weeks of age and in testes at 18 weeks of age
- Some evidence for:
  - ✓ increased proliferation of Sertoli cells
  - ✓ latent influence on sperm methylome

Overall summary

- No obvious negative effects on post pubertal semen quality or fertility
- Some positive evidence for latent effects of heifer calf nutrition on subsequent reproductive development of male progeny *in utero*
  - mediated through early follicular/oocyte development?
- No effect of PUFA supplementation on sperm production or quality
- Improved knowledge of these complex biochemical interactions
  - ✓ effective design of nutritional rearing regimens
  - ✓ identification of biomarkers for earlier sexual maturation and potentially improved fertility in the bull

Future Work

- Further investigation into underlying neuroendocrinology using integrative systems biology based approaches
- Identification of genetic variants consistent with earlier sexual maturation and improved semen quality
- *In utero* programming?

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Thank you!