

# The male reproductive system in classic galactosemia: cryptorchidism and low semen volume

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**Abstract** Previous studies examining reproductive parameters in men with galactosemia have inconsistently demonstrated abnormalities. We hypothesized that men with galactosemia may demonstrate evidence of reproductive dysfunction. Pubertal history, physical examination, hormone levels and

semen analyses were examined in 26 males with galactosemia and compared to those in 46 controls. The prevalence of cryptorchidism was higher in men with galactosemia than in the general population [11.6 % vs. 1.0 % (95%CI: 0.75–1.26;  $p < 0.001$ )]. Testosterone ( $461 \pm 125$  vs.  $532 \pm 133$  ng%;

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$p=0.04$ ), inhibin B ( $144\pm 66$  vs.  $183\pm 52$  pg/mL;  $p=0.002$ ) and sperm concentration ( $46\pm 36$  vs.  $112\pm 75\times 10^6$  spermatozoa/mL;  $p=0.01$ ) were lower and SHBG was higher ( $40.7\pm 21.5$  vs  $26.7\pm 14.6$ ;  $p=0.002$ ) in men with galactosemia compared to controls. Semen volume was below normal in seven out of 12 men with galactosemia. Men with galactosemia have a higher than expected prevalence of cryptorchidism and low semen volumes. The subtle decrease in testosterone and inhibin B levels and sperm count may indicate mild defects in Sertoli and Leydig cell function, but does not point towards severe infertility causing reproductive impairment. Follow-up studies are needed to further determine the clinical consequences of these abnormalities.

## Introduction

In 1981, Kaufman et al described the occurrence of infertility related to hypergonadotropic hypogonadism in women with classic galactosemia. Since then, several studies have focused on female patients, their pubertal development, and their fertility related problems. However, information about pubertal development and fertility in male patients is scarce and no comprehensive study has been published.

The majority of studies examining puberty, hormonal parameters and fertility are small, with a few of the males demonstrating abnormalities. In a study in young boys, three out of 12 had a history of cryptorchidism (Rubio-Gozalbo et al 2006), which suggests that the rate of cryptorchidism is higher than the expected rate of 3.68 % in the population (Berkowitz et al 1993). While pubertal development was normal in most males with classic galactosemia (Kaufman et al 1986; Kaufman et al 1981; Waggoner et al 1990), it was delayed in up to 20 % (Schweitzer et al 1993; Waggoner et al 1990). Nevertheless, testosterone, basal follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were normal in a majority of pre-pubertal and post-pubertal males (Irons et al 1986; Kaufman et al 1986; Kaufman et al 1981; Rubio-Gozalbo et al 2006; Steinmann et al 1981a, b; Waggoner et al 1990). Similarly, the LH and FSH response to luteinizing hormone releasing hormone (LHRH) was normal in the majority of adult males, and in the two cases in which baseline FSH concentration was elevated and the LHRH response was exaggerated, no clinical history was available including history of cryptorchidism (Kaufman et al 1986; Steinmann et al 1981a, b). Finally, semen analyses, the best indicator of fertility apart from pregnancy, were found to be normal in two men (Kaufman et al 1986). To our knowledge only one pregnancy has been reported in the literature for a male with galactosemia (Panis et al 2006), proving that galactosemic men are able to father a child, but thus far no thorough systematic reproductive evaluation has been done.

The paucity of data regarding pubertal development and fertility in male patients with galactosemia leads to uncertainty in counselling parents and patients about expectations around reproductive function. We tested the hypothesis that men with galactosemia would demonstrate evidence of reproductive dysfunction. To test this hypothesis, we comprehensively examined pubertal history and reproductive variables in a larger group of adult male patients with classic galactosemia.

## Materials and methods

### Patients

A total of 26 male patients with galactosemia participated in this study. Seventeen patients were included as part of a comprehensive study of adults with classic galactosemia at Children's Hospital Boston (2009), and nine in Maastricht University Medical Center (2009). None of these men participated in the previously published endocrinology study (Rubio-Gozalbo et al 2006). The male control subjects ( $n=46$ ) were recruited for a study of healthy men with normal reproductive function (Boepple et al 2008). Control men were aged 25–45 years with normal pubertal development and sexual function. All control men had testicular volumes  $\geq 15$  mL by Prader orchidometer, normal semen analysis by WHO criteria (WHO 1999) and had normal testosterone, estradiol, inhibin B, LH, FSH, thyroid stimulating hormone (TSH) and prolactin levels. The studies were approved by the Human Research Committees at Children's Hospital Boston, Massachusetts General Hospital and Maastricht University Medical Center, and all subjects gave written informed consent.

### Semi-standardized interview

A semi-standardized interview was performed, based on a list of questions. This list was translated from Dutch to English, and confirmed through translation from English back to Dutch by a separate interpreter to ensure language compatibility. Some patients participated in the interview and questionnaire only, which was conducted by telephone ( $n=5$ , Dutch patients only). All other patients were interviewed in person by CSG or CKW.

### Physical examination

All patients were examined by one of three physicians in Boston (GTB, HL and LJE) and one (CSG) in the Netherlands. Pubertal development was assessed by Tanner staging of pubic hair and penile length (Tanner and Whitehouse 1976). Testicular size was estimated by orchidometer in

Boston and ultrasound in the Netherlands using a broadband high frequency (5–12 MHz) linear array transducer (Phillips). Testicular volume was calculated by using the formula of an ellipsoid (Length x Width x Depth x  $\pi/6$ ). Measurements by orchidometer and ultrasound were cross-validated in one patient (Right testis: 15 cc versus 12.9 cc; left testis 15 cc versus 13.9 cc, respectively).

#### Laboratory measurements

Serum LH and FSH concentrations were measured using a microparticle enzyme immunoassay, as previously described (Boepple et al 2008). LH and FSH levels are expressed in IU per litre as equivalents of the pituitary standard 80/552 for LH and 92/510 for FSH. Serum testosterone concentrations were measured using a radioimmunoassay and inhibin B concentrations were measured using a double antibody enzyme linked immunosorbant assay (ELISA), as previously described (Boepple, et al 2008). Sex hormone binding globulin (SHBG) was measured using an immunochemiluminescent immunoassay (Immulite, DPC).

#### Semen analysis

Semen analyses were obtained using standard procedures and evaluated according to WHO-criteria (WHO 1999).

#### Statistical analysis

Metric data were expressed as means and standard deviations. Data that were not normally distributed were log-transformed for analysis and compared between galactosemia patients and controls using a t-test. Multiple linear regression analysis was used to examine the relationship between testosterone and age and BMI. Spearman correlation was used to examine the relationship between reproductive data within the galactosemia group. Z test was used to compare the prevalence of cryptorchidism in patients with the prevalence of cryptorchidism in the population (Berkowitz et al 1993). A p-value of <0.05 was deemed significant. The Statistical Package for Social Sciences (SPSS) version 16.0 was used for statistical analysis.

## Results

Characteristics of the patients with galactosemia are shown in Table 1. All subjects were adults with absent or barely detectable GALT activity in erythrocytes. All males with galactosemia reached Tanner stage 5 testicular size. However, there were testicular abnormalities noted in some males with galactosemia (Table 1). Three subjects, of 22

with data available, reported cryptorchidism (patients 12, 17 and 21), that persisted after birth, requiring orchidopexy between the ages of 2.5 and 11 yrs. The prevalence of cryptorchidism was increased compared to the rate of cryptorchidism at age 3 months (11.6 % vs. 1.0 % [95%CI: 0.75–1.26];  $p < 0.001$ ) ( $n = 6935$  infants) (Berkowitz et al 1993). Patient 21 also had micropenis and a hydrocoele. Three patients had hypertrophic testes upon measurement using an orchidometer; one resulting from unilateral cryptorchidism. Two of four patients from the Netherlands had low testicular volume on ultrasound, neither because of cryptorchidism, although one would have had normal testicular volume by measurement using an orchidometer. Average testicular volume was similar in men with galactosemia compared to controls (Table 2) and remained the same, on average, when the men with galactosemia and cryptorchidism were removed from the analysis ( $23.2 \pm 4.3$  vs.  $22.8 \pm 3.0$  cc, galactosemia vs. controls, respectively;  $p = 0.1$ ).

There was no difference in age between males with galactosemia and controls, although the age range of the patients with galactosemia was larger (Table 2). The BMI was significantly lower in the group with galactosemia. The mean testosterone levels were lower in patients with galactosemia, but within the reference range, with the exception of two subjects whose levels were slightly low (patients 3 and 15). There was no relationship between testosterone and age or BMI. SHBG was higher in men with galactosemia than in controls, therefore the free androgen index was lower.

Mean inhibin B was also lower in the men with galactosemia, with three subjects demonstrating inhibin B levels below the normal range. One of the subjects had a history of cryptorchidism (patient 17), one had a low testosterone but normal testicular volume (patient 15) and one had no additional abnormalities (patient 7). When inhibin B levels from males with galactosemia and cryptorchidism were removed from the analysis, levels remained lower than in control subjects ( $150 \pm 65$  vs.  $183 \pm 52$  pg/mL;  $p = 0.007$ ). Despite the lower testosterone and inhibin B levels, the mean LH and FSH levels were similar in men with galactosemia and controls.

The mean sperm concentration was lower in patients with galactosemia than controls, although only three patients fell below the lower limit (Table 1). The low sperm concentrations were found in one patient with cryptorchidism (patient 21), one with low testicular volume on ultrasound (patient 18) and one with no additional abnormalities (patient 6). Interestingly, seven out of 12 galactosemia patients had a semen volume below the reference range, whereas none of the controls did. Accounting for the low semen volume did not change the results of the sperm counts (normal vs. abnormal) for any subject. There was no relationship between sperm count, semen volume or testicular volume and timing of the onset of dietary restriction (all  $p \geq 0.5$ ).

**Table 1** Patient characteristics

Pt <sup>a</sup>	Country <sup>b</sup>	Age (yrs)	GALT gene mutation <sup>c</sup>	GALT activity <sup>d</sup>	Exposure to lactose (days)	Genital abnormalities <sup>e*</sup>	Testicular volume (cm <sup>3</sup> ) <sup>e*</sup>	Semen analysis: abnormalities <sup>e*,i</sup>	Tried to conceive a child	Pregnancies	Long term complications other than to reproductive organs <sup>e*,j</sup>
1	USA	23	Q188R/Q188R	0 %	14	No	25	Slightly low motility (46 %), 4 % normal morphology	No	–	Height
2	USA	49	Q188R/N97S	0 %	3	No	NA	Low volume (1.0 mL)	No	–	Neuro, Height, EducSib
3	USA	23	Q188R/R333Y	0 %	NA	No	25	NA	No	–	Height
4	USA	59	deletion/ deletion	0 %	60	NA	25 <sup>e</sup>	NA	No	–	Neuro, EducSib
5	USA	32	Q188R/Q188R	0 %	42	No	25 <sup>e</sup>	Low volume (1.7 mL), 1 % normal morphology	Yes	Yes, within first month	Neuro
6	USA	21	Q188R/W154X	0 %	11	No	25 <sup>e</sup>	Low volume (0.8 mL), low concentration (2.1 million/mL), low motility (22 %), 0 % normal morphology	No	–	Neuro
7	USA	21	K285N/L195P	0 %	NA	No	NA	NA	No	–	–
8	USA	33	Q188R/K285N	0 %	180	No	NA	Low volume (1.2 mL)	No	–	Neuro, Height, EducPar, EducSib
9	USA	35	Q188R/Q188R	0 %	60	No	25 <sup>e</sup>	NA	No	–	Neuro, Height, EducPar, EducSib
10	USA	29	Q188R/K285N	0 %	7	No	25	NA	No	–	Neuro, EducPar, EducSib
11	USA	25	Q188R/deletion	0 %	9	No	25	NA	No	–	Neuro, EducPar, EducSib
12	USA	27	Q188R/Q188R	0 %	1	Cryptorchidism	NA	NA	No	–	–
13	USA	25	K127Q/ deletion	0 %	NA	No	NA	NA	No	–	Height
14	USA	22	Q188R/ deletion	0 %	6	No	NA	Low volume (0.2 mL)	No	–	Neuro (no sibs)
15	USA	45	Q188R/Q188R	0 %	7	No	25	NA	No	–	Height
16	USA	52	Q188R/Q188R	0 %	20	NA	25	Low volume (0.7 mL)	Yes	Yes, within first month	Height, EducPar
17	USA	45	Q188R/Q188R	0 %	9	Unilateral cryptorchidism	15 <sup>f</sup>	NA	Yes	No, despite 36 months trying	– (no sibs)
18	NL	21	NA <sup>c</sup>	0.3 %	28	No	13.4 <sup>g,h</sup>	Low concentration (16.6 million/mL), low motility (30 %)	No	–	– (neuro NA, no sibs)
19	NL	22	NA	0.4 %	7	No	12.8 <sup>g,h</sup>	None	No	–	– (neuro NA, no sibs)
20	NL	21	NA	1.3 %	14	No	23.1 <sup>g</sup>	None	No	–	EducPar, EducSib (neuro NA)
21	NL	24	NA	1.9 %	4	Cryptorchidism, micropenis, hydrocoele	20.4 <sup>g</sup>	Low volume (0.8 mL), azoospermia (concentration: 0 million/mL)	No	–	EducPar (neuro NA)
22	NL	26	NA	NA	17	No	NA	NA	No	–	Height, EducPar, EducSib (neuro NA)
23	NL	22	NA	NA	0	NA	NA	NA	No	–	EducPar (neuro NA, no sibs)
24	NL	19	NA	NA	10	No	NA	NA	No	–	EducPar, EducSib (neuro NA)

**Table 1** (continued)

Pt <sup>a</sup>	Country <sup>b</sup>	Age (yrs)	GALT gene mutation <sup>c*</sup>	GALT activity <sup>d</sup>	Exposure to lactose (days)	Genital abnormalities <sup>e*</sup>	Testicular volume (cm <sup>3</sup> ) <sup>e*</sup>	Semen analysis: abnormalities <sup>e*,i</sup>	Tried to conceive a child	Pregnancies	Long term complications other than to reproductive organs <sup>e*,j</sup>
25	NL	21	NA	NA	75	NA	NA	NA	No	–	EducPar, EducSib (neuro NA)
26	NL	25	NA	NA	70	No	NA	NA	No	–	Height, EducSib (neuro NA)

<sup>a</sup> Pt=Patient number

<sup>b</sup> USA =United States, NL=The Netherlands

<sup>c\*</sup> NA =Not available

<sup>d</sup> GALT activity was measured using the LC-MS/MS method as described by Li et al (2010) in the American patients, and by the method of Lindhout et al (2010) in the Dutch patients

<sup>e</sup> The examining physician estimated the testes volume higher than 25 cm<sup>3</sup> in this patient

<sup>f</sup> Average size; right 25 cc (estimated to be higher), left 5 cc

<sup>g</sup> Measured on ultrasound

<sup>h</sup> Low (normal 15–25 cm<sup>3</sup>)

<sup>i</sup> Normal WHO parameters: Volume 2–5 mL, count 20–500 million/mL, motility 50–100 %, morphology 5–100 %, total sperm count >40 million

<sup>j</sup> Neuro =neurological abnormalities including ataxia, tremor; Height =Height is lower than 9 cm below target height (no subject was more than 9 cm above target height); EducPar =Education is below level of parents; EducSib =Education is below level of sibs

## Discussion

This comprehensive examination of reproductive parameters in men with galactosemia demonstrates a low semen volume and an increased prevalence of cryptorchidism. In addition, testosterone, inhibin B and sperm concentration were lower and SHBG was higher than in control subjects, although all were within the normal range on average. Gonadotropin levels were normal. These data suggest that men with galactosemia have unique abnormalities in seminal fluid production. In addition, there is evidence for both mild Sertoli and Leydig cell dysfunction in the testes. However, the clinical significance of these abnormalities, with the exception of cryptorchidism, would have little impact on fertility.

In accordance with an earlier study examining an independent cohort (Rubio-Gozalbo et al 2006), the prevalence of cryptorchidism was increased in men with galactosemia compared to the prevalence in the general population at 3 months of age. The higher rate was not related to premature birth. Noting cryptorchidism in men with galactosemia will be important not only to confirm the findings, but also to ensure early treatment both for fertility preservation and to avoid the increased risk of testicular cancer.

The mechanism for the increased prevalence of cryptorchidism is not clear. Testicular descent occurs in two phases (Hughes and Acerini 2008). In the first phase, the cranio-suspensory ligament regresses under the influence of androgens, causing the testes to migrate through the abdomen. Simultaneously, the gubernaculum testis thickens under the control of androgens and insulin-like 3 (INSL3) and its receptor, leucine-rich repeat-containing G-protein-coupled receptor 8 (LGR8). Androgen deficiency is a common cause of cryptorchidism often associated with micropenis or hypospadias (Deeb et al 2005), but subjects in the current study had normal testosterone levels, including those with cryptorchidism and micropenis. Alternatively, perturbation of normal protein glycosylation by galactose could play a role. Glycosylation abnormalities are more prominent in untreated patients with galactosemia (Charlwood et al 1998) and galactose, as along with its derivative metabolites, are many times higher in the galactosemic fetus when testicular descent occurs. LGR8 is N-linked glycosylated

**Table 2** Age, BMI, testicular and hormonal values in patients with galactosemia and controls

	Reference values	Control group (n=46)		Galactosemia patients (n=26)		P value	Number of galactosemia patients included
		Mean ± SD	Range	Mean ± SD	Range		
Age		28.7±6.1	(19–41)	29.0±11	(19–59)	0.9	26
BMI	20–25 kg/m <sup>2</sup>	25.5±4.0	(19.5–35.9)	23.3±3.7	(18.3–34.7)	0.03	17
Testicular volume	15–25 cm <sup>3</sup> (orchidometer)	22.8±3.0	(15–25 <sup>a</sup> )	22.3±4.6	(12–25 <sup>a</sup> )	0.4	12
Testosterone	280–1,170 ng%	532±133	(349–941)	461±125	(230–720)	0.04	22
SHBG	13–71 nmol/L	26.7±14.6	(3.1–59)	40.7±21.5	(15–102)	0.002	22
Free androgen index (FAI)	3–35	12.1±2.8	(7.2–20)	8.1±1.6	(4.7–12)	<0.001	22
Inhibin B	88–432 pg/mL	183±52	(92–355)	144±66	(49–359)	0.002	22
LH	1.14–8.75 mIU/mL	3.8±1.2	(4.9–17.9)	3.9±1.5	(2.2–7.5)	1.0	22
FSH	0.95–11.95 mIU/mL	2.9±1.1	(1.8–9.7)	3.8±2.5	(1.2–10.8)	0.2	22
Sperm Concentration	≥ 20×10 <sup>6</sup> spermatozoa/mL	112±75	(20–314)	46±36	(0–106)	0.01	12

<sup>a</sup> When the examining physician estimated the volume higher than 25 cm<sup>3</sup>, 25 cm<sup>3</sup> is used for analysis corresponding to the largest bead on the orchidometer

(Hsu 2003) and its closest relative, LGR7, requires glycosylation for normal receptor function (Yan et al 2008). Therefore, hypoglycosylation could play a role in abnormal testicular descent in these patients.

The sperm count was lower, on average, in men with galactosemia than in controls. Several environmental factors, such as chemicals that have estrogenic effects, may influence sperm concentration, testes descent and testosterone levels (Messina 2010). In particular soy milk, which many patients with galactosemia consume in place of milk, is a phytoestrogen with potential estrogenic influence. Although the start of soy milk ingestion is too late to influence testes descent, the slightly lower sperm concentration in males with galactosemia could be related to the consumption of soy milk (Chavarro et al 2008). Further studies on the effect of soy on semen parameters in males are needed as no large, properly controlled intervention studies have been performed (Chavarro et al 2008; Messina 2010).

One of the most remarkable results in the semen analysis is the low semen volume noted in seven of 12 patients. Although a low volume in itself does not lead to fertility problems, the finding is unusual, and may provide insight into pathophysiological mechanisms in this disease. The contribution of prostate and the seminal vesicle fluid accounts for total semen volume. Testosterone levels affect seminal vesicle fluid volume (Mann and Mann 1981), but were normal in the majority of men in the current study, making it unlikely that low testosterone contributed to the low volume. Another potential mechanism to explain these data may therefore involve endogenous galactose synthesis within the cells of the seminal vesicles that are responsible for the synthesis of fructose and the bulk of seminal fluid production (Hers 1956). Fructose and sorbitol are the main

osmotic factors in seminal vesicle fluid. Concentrations of fructose in normal seminal fluid are very high. The polyol pathway consisting of aldose reductase (AR, EC 1.1.1.2.1) and sorbitol dehydrogenase (SDH, EC 1.1.1.14) is uniquely responsible for the synthesis of fructose in the male reproductive tract (Frenette et al 2006). While sorbitol is the preferred substrate for SDH, mediating its conversion to fructose, galactose is a better substrate for AR than glucose (Berry 1995). Thus, endogenously synthesized galactose in seminal vesicle cells of patients with severe GALT deficiency may inhibit AR-mediated conversion of glucose to sorbitol, in effect reducing the synthesis of fructose from sorbitol via SDH. If so, one would predict that galactitol would be elevated in semen from patients with galactosemia while fructose and sorbitol are decreased. Thus, the number of osmotically active molecules in semen of galactosemic patients may be lower possibly resulting in a lower volume. Unfortunately, the fructose concentrations in these samples were not measured, but we propose that future research should examine this intriguing finding more closely.

As in previous studies, the majority of men with galactosemia had normal testosterone levels. Only two men had levels that fell below the normal range for the assay, but samples were obtained in the afternoon when testosterone tends to be lower. Further, LH levels were not elevated. Interestingly, the SHBG levels were higher in the men with galactosemia, resulting in a lower free androgen index. Nevertheless, the clinical relevance of the finding is likely to be minimal.

Inhibin B levels were lower on average than in the controls. Inhibin B correlates with Sertoli cell number and the level of spermatogenesis (McNeilly 2012). Consistent with lower inhibin B levels, the male patients with galactosemia had a lower average sperm concentration than controls.

Nevertheless, only three men with galactosemia had inhibin B levels that fell below the normal range. Cryptorchidism clearly explains azoospermia and low inhibin B in one of the men. The other two subjects had normal testicular volumes although one also had a low testosterone. Taken together with the lower testosterone levels, data may indicate a very subtle defect in Leydig and Sertoli cell function in men with galactosemia, although in the non-cryptorchid testes, they are unlikely to reflect decreased fertility.

The mild reproductive abnormalities identified in the current study would not be expected to affect fertility, yet there is a paucity of data documenting fertility in men with galactosemia. Including the current subjects, there are three fathered pregnancies in the literature (Panis et al 2006), compared to more than 60 published pregnancies in women (Gubbels et al 2008). The lack of documented paternity in men with galactosemia may be related to a publication bias or difficulty documenting paternity. Men with galactosemia who attempt pregnancy may not seek special medical care unlike women for whom ovarian problems can be a reason for continuing regular surveillance in adult life. Most likely social reasons account for absence of paternity based on the known social interaction problems (Bhat et al 2005; Bosch et al 2004) and delayed psychosocial development documented in these men (Gubbels et al 2011).

In conclusion, this study was performed to bridge the gap of knowledge on fertility of men who suffer from classic galactosemia. We have demonstrated that men with galactosemia show subclinical and biochemical alterations in the reproductive tract that may be related to their disease, although most men will not experience fertility problems and the clinical relevance of the subtle decrease in testosterone and inhibin B levels and sperm count remains to be determined. Our paper does not provide an explanation for the low number of men with galactosemia who have fathered a child, and we believe a psychosocial factor may more likely be involved than reproductive failure. The higher than expected number of men with cryptorchidism in their medical history remains a concern and the relationship between galactosemia and undescended testes needs to be elucidated. Finally, the finding that men with classic galactosemia have low semen volumes may not have direct consequences for fertility, but this finding might provide further insight into the pathophysiology of galactosemia.

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## References

- Berkowitz GS, Lapinski RH, Dolgin SE, Gazella JG, Bodian CA, Holzman IR (1993) Prevalence and natural history of cryptorchidism. *Pediatrics* 92(1):44–49
- Berry GT (1995) The role of polyols in the pathophysiology of hypergalactosemia. *Eur J Pediatr* 154(7 suppl 2):S53–S64
- Bhat M, Haase C, Lee PJ (2005) Social outcome in treated individuals with inherited metabolic disorders: Uk study. *J Inherit Metab Dis* 28(6):825–830
- Boepple PA, Hayes FJ, Dwyer AA, Raivio T, Lee H, Crowley WF Jr, Pitteloud N (2008) Relative roles of inhibin b and sex steroids in the negative feedback regulation of follicle-stimulating hormone in men across the full spectrum of seminiferous epithelium function. *J Clin Endocrinol Metab* 93(5):1809–1814
- Bosch AM, Grootenhuys MA, Bakker HD, Heijmans HS, Wijburg FA, Last BF (2004) Living with classical galactosemia: health-related quality of life consequences. *Pediatrics* 113(5):e423–e428
- Charlwood J, Clayton P, Keir G, Mian N, Winchester B (1998) Defective galactosylation of serum transferrin in galactosemia. *Glycobiology* 8(4):351–357
- Chavarro JE, Toth TL, Sadio SM, Hauser R (2008) Soy food and isoflavone intake in relation to semen quality parameters among men from an infertility clinic. *Hum Reprod* 23(11):2584–2590
- Deeb A, Mason C, Lee YS, Hughes IA (2005) Correlation between genotype, phenotype and sex of rearing in 111 patients with partial androgen insensitivity syndrome. *Clin Endocrinol (Oxf)* 63(1):56–62
- Frenette G, Thabet M, Sullivan R (2006) Polyol pathway in human epididymis and semen. *J Androl* 27(2):233–239
- Gubbels CS, Land JA, Rubio-Gozalbo ME (2008) Fertility and impact of pregnancies on the mother and child in classic galactosemia. *Obstet Gynecol Surv* 63(5):334–343
- Gubbels CS, Maurice-Stam H, Berry GT, Bosch AM, Waisbren S, Rubio-Gozalbo ME (2011) Psychosocial developmental milestones in men with classic galactosemia. *J Inherit Metab Dis* 34(2):415–419
- Hers HG (1956) Le mécanisme de la transformation de glucose en fructose par les vésicules séminales. *Biochim Biophys Acta* 22(1):202–203
- Hsu SY (2003) New insights into the evolution of the relaxin-Igr signaling system. *Trends Endocrinol Metab* 14(7):303–309
- Hughes IA, Acerini CL (2008) Factors controlling testis descent. *Eur J Endocrinol* 159(Suppl 1):S75–S82
- Irons M, Levy HL, Crowley W (1986) Gonadal function in galactosemia. *Am J Hum Genet* 39:A13
- Kaufman FR, Kogut MD, Donnell GN, Goebelsmann U, March C, Koch R (1981) Hypergonadotropic hypogonadism in female patients with galactosemia. *N Engl J Med* 304(17):994–998
- Kaufman FR, Donnell GN, Roe TF, Kogut MD (1986) Gonadal function in patients with galactosaemia. *J Inherit Metab Dis* 9(2):140–146
- Li Y, Ptolemy AS et al (2010) Quantification of galactose-1-phosphate uridylyltransferase enzyme activity by liquid chromatography-tandem mass spectrometry. *Clin Chem* 56(5):772–780
- Lindhout M, Rubio-Gozalbo ME et al (2010) Direct non-radioactive assay of galactose-1-phosphate:uridylyltransferase activity using high performance liquid chromatography. *Clin Chim Acta; International Journal of Clinical Chemistry* 411(13-14):980–983
- Mann T, Mann CL (1981) Male reproductive function and semen: themes and trends in physiology, biochemistry and investigative andrology. New York, Springer-Verlag
- McNeilly AS (2012) Diagnostic applications for inhibins and activins. *Mol Cell Endocrinol* 359(1–2):121–125

- Messina M (2010) Soybean isoflavone exposure does not have feminizing effects on men: a critical examination of the clinical evidence. *Fertil Steril* 93(7):2095–2104
- Panis B, Bakker JA, Sels JP, Spaapen LJ, van Loon LJ, Rubio-Gozalbo ME (2006) Untreated classical galactosemia patient with mild phenotype. *Mol Genet Metab* 89(3):277–279
- Rubio-Gozalbo ME, Panis B, Zimmermann LJI, Spaapen LJ, Menheere PPCA (2006) The endocrine system in treated patients with classical galactosemia. *Mol Genet Metab* 89(4):316–322
- Schweitzer S, Shin Y, Jakobs C, Brodehl J (1993) Long-term outcome in 134 patients with galactosaemia. *Eur J Pediatr* 152(1):36–43
- Steinmann B, Gitzelmann R, Zachmann M (1981a) Galactosemia: hypergonadotropic hypogonadism already found in prepubertal girls but only in adult males. *Eur J Pediatr* 135:337
- Steinmann B, Gitzelmann R, Zachmann M (1981b) Hypogonadism and galactosemia. *N Engl J Med* 305(8):464–465
- Tanner JM, Whitehouse RH (1976) Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child* 51(3):170–179
- Waggoner DD, Buist NR, Donnell GN (1990) Long-term prognosis in galactosaemia: results of a survey of 350 cases. *J Inherit Metab Dis* 13(6):802–818
- WHO (1999) WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction, 4th edn. Cambridge University Press, Cambridge, UK
- Yan Y, Scott DJ, Wilkinson TN, Ji J, Tregear GW, Bathgate RA (2008) Identification of the n-linked glycosylation sites of the human relaxin receptor and effect of glycosylation on receptor function. *Biochemistry* 47(26):6953–6968