REVIEW

Pathophysiology and management of classic galactosemic primary ovarian insufficiency

Synneva Hagen-Lillevik1,2,*, John S Rushing3,*, Leslie Appiah4, Nicola Longo1,2, Ashley Andrews1, Kent Lai1,2 and Joshua Johnson3,3

1Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah, USA
2Department of Nutrition and Integrative Physiology, University of Utah College of Health, Salt Lake City, Utah, USA
3Divisions of Reproductive Sciences, Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Colorado Denver (AMC), Aurora, Colorado, USA
4Division of General Obstetrics and Gynecology, Department of Obstetrics and Gynecology, University of Colorado Denver (AMC), Anschutz Outpatient Pavilion, Aurora, Colorado, USA

Correspondence should be addressed to K Lai or J Johnson: kent.lai@hsc.utah.edu or joshua.2.johnson@ucdenver.edu

*(S Hagen-Lillevik and J S Rushing contributed equally to this work)

Abstract

Classic galactosemia is an inborn error of carbohydrate metabolism associated with early-onset primary ovarian insufficiency (POI) in young women. Our understanding of the consequences of galactosemia upon fertility and fecundity of affected women is expanding, but there are important remaining gaps in our knowledge and tools for its management, and a need for continued dialog so that the special features of the condition can be better managed. Here, we review galactosemic POI and its reproductive endocrinological clinical sequelae and summarize current best clinical practices for its management. Special consideration is given to the very early-onset nature of the condition in the pediatric/adolescent patient. Afterward, we summarize our current understanding of the reproductive pathophysiology of galactosemia, including the potential action of toxic galactose metabolites upon the ovary. Our work establishing that ovarian cellular stress reminiscent of endoplasmic reticulum (ER) stress is present in a mouse model of galactosemia, as well as work by other groups, are summarized.

Lay summary

Patients with the condition of classic galactosemia need to maintain a strict lifelong diet that excludes the sugar galactose. This is due to having mutations in enzymes that process galactose, resulting in the buildup of toxic metabolic by-products of the sugar. Young women with classic galactosemia often lose the function of their ovaries very early in life (termed ‘primary ovarian insufficiency’), despite adherence to a galactose-restricted diet. This means that in addition to the consequences of the disease, these women also face infertility and the potential need for hormone replacement therapy. This article summarizes current strategies for managing the care of galactosemic girls and women and also what is known of how the condition leads to early primary ovarian insufficiency.

Key Words: ▶ primary ovarian insufficiency ▶ ovary ▶ follicle ▶ reproductive endocrinology ▶ fertility preservation

Reproduction and Fertility (2021) 2 R67–R84
Introduction

Classic galactosemia is an inborn error of carbohydrate metabolism associated with early-onset primary ovarian insufficiency (POI) in young women. Our understanding of the consequences of galactosemia upon fertility and fecundity of affected women is expanding, but there are important remaining gaps in our knowledge and tools for its management. For example, while clinical consensus is building about how best to manage patients with galactosemia in prepubertal life and the reproductive years, there is a general lack of established ‘best practice’ strategies. These gaps also include open questions about the mechanism(s) by which galactosemic metabolic perturbations impact reproductive organs, in particular, the ovary. Indeed, systemic production of ‘toxic metabolites’ of galactosemia is often referenced as a causal factor in compromised physiology generally, but direct evidence that individual metabolites can induce ovarian damage has been elusive. In this review, we attempt to fill in some of these gaps. First, we review the condition and its reproductive endocrinological clinical sequelae and summarize current best clinical practices for the management of this quite severe, early-onset POI. Afterward, we set out the state of our understanding of the reproductive pathophysiology of galactosemia, including the potential action of toxic galactosemic metabolites on the ovary. Our work establishing that ovarian cellular stress reminiscent of endoplasmic reticulum (ER) stress is present in a mouse model of galactosemia, as well as work by other groups, are summarized in this latter review section.

Classic galactosemia

Galactosemia results in the deficiency of enzymes in the Leloir pathway (Holden et al. 2003) including galactokinase (GALK1), galactose-1-phosphate uridylyltransferase (GALT), galactose mutarotase (GALM), or UDP-galactose 4'-epimerase (GALE), any of which can compromise the metabolism of galactose (Wada et al. 2019). The most common and severe form of galactosemia is GALT deficiency, also called classic galactosemia (CG), and affects 1/14,000–1/80,000 individuals worldwide (Jumbo-Lucioni et al. 2012) and 1:53,554 births in the United States of America (Therrell et al. 2014). CG is inherited in an autosomal recessive pattern. Newborns in many countries are screened through screening programs for CG after birth by measuring GALT enzyme activity or galactose in dried blood spots. Infants that screen positive have further diagnostic testing to allow a timely diagnosis early in life. Diagnosis of CG includes detection of reduced GALT enzyme activity in red blood cells, elevated erythrocyte galactose-1-phosphate (gal-1P) levels, and, in general, the identification of pathogenic variants in the GALT gene (Pyhtila et al. 2015). Initial symptoms for infants include emesis and poor feeding with failure to thrive, lethargy, jaundice, liver failure, and Gram-negative sepsis. Infants who survive the acute presentation or are treated early because of newborn screening still suffer chronic long-term complications including developmental delay, speech and language delays, motor function abnormalities, cataracts, absent or delayed puberty or premature menopause as a result of ovarian insufficiency (Fridovich-Keil et al. 2011, Berry 2020).

Treatment for CG includes a galactose-restricted diet to avoid exposure to sugar. This results in the reduction, but not in the normalization of metabolites that accumulate inappropriately due to the deficiency of the GALT enzyme. The metabolites galactitol and gal-1P are known to have toxic effects upon cells and are thought to contribute to CG pathophysiology (Thakur et al. 2017). Dietary galactose restriction resolves initial neonatal symptoms, but chronic complications persist with varying prevalence and severity despite adherence to dietary management. Although a galactose-restricted diet is started as soon as the diagnosis is confirmed, the exact timing of diet initiation does not have long-term effects on the development of chronic conditions later in life (Jumbo-Lucioni et al. 2012).

The persistent elevation of galactitol and gal-1P is likely due to the endogenous galactose production from UDP-galactose via UPD-glucose, which results in elevated levels of galactose, galactitol, and gal-1P in CG patients despite being on a galactose-restricted diet (Berry et al. 2004). Mean plasma galactose levels in CG patients on a galactose-restricted diet are on average 2.72 ± 0.70 μM (0.05 ± 0.01 mg/dL) compared to 0.52 ± 0.08 μM (0.01 ± 0.001 mg/dL) in non-galactosemic subjects on a lactose-free diet (Ning & Segal 2000); red blood cell gal-1P levels ranges from 1.1–3.5 mg/dL (0.04–0.13 mM) as compared to < 1 mg/dL (<0.038 mM) in non-galactosemic individuals (Berry et al. 1997).

Complications of classic galactosemia

Beginning in infancy, individuals with CG are assessed periodically for cognitive development, neurological and motor functions, speech and language delays, psychosocial development, bone health, and cataracts (Welling et al. 2017). Further, gal-1P levels are checked regularly to determine dietary compliance, and adjustments are made
for elevated levels. An observational study that included 33 adult participants (17 men and 16 women) with CG on a galactose-restricted diet found the following complications affecting participants: cataracts (21%), low bone density (24%), tremor (46%), ataxia (15%), dysarthria (24%), and apraxia of speech (9%) (Waisbren et al. 2012).

**Primary ovarian insufficiency in classic galactosemia**

POI is one of the most common chronic complication associated with CG and affects 80–90% of female patients following a galactose-restricted diet (Fridovich-Keil et al. 2011). POI is defined as amenorrhea greater than 3 months in young adolescents and adult women who are less than 40 years of age with two follicle-stimulating hormone (FSH) levels in the menopausal range within a month of testing and decreased serum estradiol levels (Nelson 2009). POI can lead to infertility, hypoestrogenism, as well as mental distress (Nelson 2009).

The hypoestrogenic environment resulting from POI can result in poor bone health with an increased risk of fracture (Marino & Misra 2011, Batey et al. 2013), heightened risk of cardiovascular events (Roeters Van Lennep et al. 2016), and menopausal symptoms (Sullivan et al. 2016). Estrogen is the primary hormone that promotes secondary sexual characteristics that develop during puberty such as breasts, bone maturation, uterine growth, and the onset of menses. Many females with POI before pubertal onset will not develop these secondary sex characteristics. Hormone replacement therapy (HRT) with estrogen and progesterone is the mainstay treatment for patients with POI (see also ‘Management,’ subsequently).

**The onset of primary ovarian insufficiency in classic galactosemia**

Increasing evidence in CG POI suggests female infants have normal-appearing ovaries at birth that become damaged over time. A review of gonadal function in patients with CG by Rubio-Gozalbo and colleagues in 2010 included 23 female patients whose ovaries were evaluated either histologically, by imaging, or laparoscopy (Rubio-Gozalbo et al. 2010). Of the 23 patients, two were neonates and had morphologically normal ovaries with numerous oocytes (Levy et al. 1984, Levy 1996). The remaining patients, excluding one, were > of age and all but two had hypoplastic ovaries, and evidence of ovarian dysfunction with either fibrous ovarian tissue, significantly diminished primordial follicles, or absent growing follicles (Rubio-Gozalbo et al. 2010). There was a single patient that had normal-appearing ovaries at the age of seven, but repeat laparoscopy at age 17 revealed streak gonads (Kaufman et al. 1981). These findings are consistent with recent data from ovarian tissue cryopreservation (OTC) in prepubertal CG patients. Six prepubertal girls with CG underwent ovarian tissue cryopreservation for fertility preservation; five of the girls were less than five years of age and had absent ovarian follicles (Mamsen et al. 2018). This further suggests that females with CG have normal oocyte numbers during infancy and early childhood with rapid loss over time. The trajectory of gonadotrophins to mirror menopausal levels throughout childhood into adolescence can further corroborate the biopsy/ultrasounds and suggest a progression of ovarian failure; although evidence of abnormal gonadotrophin levels have been seen as early as nine months in galactosemia (Kaufman et al. 1981, Levy et al. 1984). A retrospective chart review of 11 females with CG followed by our clinic was conducted. When available, information regarding genotype, the timing of menses/amenorrhea, the use of HRT and labs including gal-1P, FSH, anti-Müllerian hormone (AMH), luteinizing hormone (LH) and estradiol were recorded longitudinally for each patient. Our data revealed nine of 11 patients with evidence of POI including abnormal hormonal values. Of those nine patients, FSH levels before and after the age of 10 were available for six patients (summarized in Fig. 1). Four of the six had normal/borderline FSH levels prior to age 10 that sharply increased at age 10. The other two patients had elevated FSH levels prior to age 10. Six patients had data for AMH, with only two showing normal/high AMH levels before age 10 or when measured (Table 1).

![Figure 1 Longitudinal follicle-stimulating hormone (FSH) levels for female patients with classic galactosemia (CG). FSH levels are provided for a cohort of child and adolescent CG patients. The green shaded region represents normal values. The timing of hormone replacement initiation was not available for this patient set; this may have influenced FSH levels in some patients.](https://raf.bioscientifica.com)
While 32–55% of patients with CG do not achieve spontaneous menarche, a fraction that do can cycle regularly into their late 20s (van Erven et al. 2017, Frederick et al. 2018). Most cases of POI in CG are diagnosed in the preteen to teenage years due to ovarian insufficiency not being clinically evident until puberty (Fridovich-Keil et al. 2011). In a recent study that evaluated these parameters in the largest cohort of patients with CG to date, 68% of the 102 postpubertal females with CG achieved spontaneous menarche. Spontaneous menarche occurred at an average age of 13.8 years (range 10–19), and HRT-assisted menarche was 14.2 years (range 11–18) (Frederick et al. 2018). If spontaneous menarche was achieved, only 50% of patients still cycled regularly after three years, 35% after five years, and fewer than 15% had regular menstrual cycles after 10 years. In the patients that did not receive HRT, approximately one-third of the 102 patients with CG had regular menstrual cycles in their late teens, and the number decreased to approximately 10% by their mid-20s (Frederick et al. 2018). In our small set of patients (Table 1), the majority did achieve spontaneous menarche, but only 50% were still cycling regularly after age 16 without the use of hormonal therapies (Table 1).

Due to the variability in the timing of POI onset among CG patients, and the lack of a reliable early screening tool for ovarian function/ovarian reserve, patients are often not officially diagnosed with POI until their peri-pubertal years when secondary sexual characteristics are absent (see also subsequent section). This makes counseling and prospective management of POI in CG difficult. Even so, some potential risk factors for the development of POI in CG patients have been identified. For example, there is a higher probability of POI and other long-term complications if the GALT mutation is Q188R/Q188R (Guerrero et al. 2000) or if the mean erythrocyte gal-1P is > 2.0 mg/dL on a galactose-restricted diet (Yuzuk et al. 2018). The p.Q188R mutation is one of the most prevalent missense mutations in the GALT gene that leads to higher instability of the protein (Kumar et al. 2020). In addition to POI, homozygous Q188R mutations are also associated with cognitive impairment and verbal dyspraxia (Robertson et al. 2000, Antshel et al. 2004).

### Pathophysiology of primary ovarian insufficiency

Oocytes, which are located within ovarian follicles, are progressively lost throughout the female life cycle. The maximum number of oocytes (approximately 6–7 million) is before birth at around 20 weeks gestation, which is also when primordial follicles begin to form. At birth, there are approximately 1–2 million oocytes that drop to 300,000–400,000 at puberty, and only 400–500 are ovulated during a lifespan (Strauss III & Williams 2019). Oocytes are female
Folliculogenesis and cellular signaling pathways

To delineate the potential pathophysiology of ovarian demise in CG, it is important to appreciate the normal lifespan of the ovary and follicle development. Folliculogenesis occurs in essentially four stages, beginning with the transition of a primordial follicle to the primary follicle, then to a secondary, antral, and finally, preovulatory follicle. Even in healthy ovaries, the vast majority of oocytes and follicles will not achieve ovulation but will die by atresia (Liu et al. 2006, Adhikari & Liu 2009). In utero, primordial follicles undergo melosis and remain arrested at prophase I of the cell cycle. At around 24 weeks gestation, the first wave of primordial follicles become activated and grow into primary follicles, and after birth, the majority grow and are arrested at the pre-antral stage. At puberty, gonadotrophin production begins and selected follicles can progress to the antral stage with a select number maturing to ovulate an oocyte (Ford et al. 2020). The growth of primordial follicles to ultimately ovulatory follicles is a continuous process throughout a woman’s reproductive life, and the number of primordial follicles is considered the ovarian reserve; thus, the appropriate timing is integral in preserving ovarian function until anticipated menopause.

Various animal models of POI and cultured human ovaries have elucidated different signaling pathways involved in folliculogenesis at different stages of development; of note for this review are the phosphatidylinositol 3-kinase/AKT signaling pathway (PI3K/AKT), and the unfolded protein response (UPR), specifically EIF2A phosphorylation (Ernst et al. 2017). Many other well-known signaling pathways, including nuclear receptor signaling (Komatsu & Masubuchi 2017), and the NFKB pathway (Wright et al. 2020) have all been shown to regulate normal folliculogenesis. Here, we will limit our discussion to signaling pathways that have been investigated in the context of ovarian dysregulation in the CG mouse model.

Tightly regulated control of PI3K/AKT signaling is paramount for proper initiation of follicle growth and primordial follicle survival (Liu et al. 2006). Loss of regulators of PI3K/AKT signaling such as Pten, Foxo3a, Pdk1, and Tsc 1/2 in mouse oocytes and granulosa cells can lead to abnormal activation of primordial follicles, and thus, POI with depletion of the ovarian reserve (John et al. 2008, Jagarlamudi et al. 2009, Reddy et al. 2009, Adhikari et al. 2010). Disruption of upstream regulators of PI3K/AKT such as semaphorin 6C (SEMA6C) and cell division cycle 42 (CDC42) can also influence follicle activation through PI3K/AKT signaling (Van et al. 2018, Zhou et al. 2018). The phosphorylation of AKT is central in PI3K/AKT signaling and controls growth in the cell. In mice with Pten deleted in their oocytes, increased pAKT was associated in a stage-specific manner with the mass activation of follicles (Jagarlamudi et al. 2009). Additionally, stimulation of AKT phosphorylation and inhibition of PTEN in cortical fragments of ovaries from human patients receiving chemotherapy were able to activate primordial follicles and produced two live human births (Kawamura et al. 2013, Suzuki et al. 2015). Changes in PI3K/AKT signaling are also associated with a high-fat diet; Nteeba and coworkers saw increased levels of mRNA for AKT and Kit ligand indicating enhanced PI3K/AKT signaling in older mice after a high-fat diet (Nteeba et al. 2013). While PI3K/AKT signaling is involved in the activation and growth of follicles, the exact mechanism and timing of activity in this pathway are poorly understood.

The UPR is a time-dependent, paradoxical survival or death response in the cell in response to ER stress that culminates in either the cell restoring homeostasis or dying via apoptosis and/or autophagy (Donnelly et al. 2013). Improper folding of proteins (a surge of protein synthesis), abnormalities in glycosylation, increased oxidative stress, and perturbations of Ca²⁺ homeostasis are all activators of ER stress and the UPR (Osłowski & Urano 2011). Harada et al. 2020).
and coworkers found evidence of increased UPR molecular markers in the granulosa cells of late secondary follicles in mice suggesting a normal physiological role of UPR in meeting the needs of increased protein synthesis as the follicle nearing maturation (Harada et al. 2015). True to the roles of the UPR as both pro-survival and death promoter, in goat ovaries, ER stress marker protein BiP was present in both atretic and non-atretic granulosa cells but increased in the granulosa cells of follicles destined for atresia; early atretic follicles also showed increased BiP (Lin et al. 2012). In contrast, the apoptosis marker CHOP was only present in granulosa cells of atretic follicles (Lin et al. 2012). In vitro and in vivo models of obesity-induced POI exhibited increased ER stress markers and saw less viable oocytes ovulated; administration of a UPR modulator (Salubrinal) reversed these poor outcomes (Wu et al. 2010, 2012, 2015). As the UPR is a phenomenon in both follicle growth and atresia, any disruption of the UPR likely will be detrimental to the oocyte, follicles, and ovarian health (Lin et al. 2012, Babayev et al. 2016, Xiong et al. 2017, Takehara et al. 2020).

One key regulator of the UPR is the phosphorylation of EIF2A. In times of cellular stress, the phosphorylation of EIF2A serves to slow down protein translation in the cell to restore homeostasis (Donnelly et al. 2013). Beyond the UPR, EIF2A is an important component of normal protein translation, specifically to the 43S pre-initiation complex which acts with the EIF4F complex to initiate synthesis of new polypeptides during cellular growth (Colegrove-Otero et al. 2005). The phosphorylation of EIF2A by various kinases blocks the initiation of protein translation by inhibiting EIF2B, the nucleotide exchange factor involved in the 43S pre-initiation complex (Donnelly et al. 2013). In the oocyte, phosphorylated EIF2A appears to be involved in regulating meiosis and keeping follicles dormant until their predestined activation (Le Bouffant et al. 2008, Alves et al. 2009). As keeping the lifespan of follicles dormant is critical for ovarian longevity, EIF2A regulation is likely a key player in developing POI. In humans, mutations in EIF4ENIF1, an important transport protein for components crucial to the EIF4F complex, result in POI (Kasippilai et al. 2013, Zhao et al. 2019). Mutations in EIF2B are also associated with POI with concurrent neurological complications, providing more evidence that protein initiation factors are involved in maintaining ovarian health (Fogli et al. 2004).

**Human and animal model examples**

POI is associated with a variety of different conditions such as X chromosome abnormalities (Turner syndrome, FMR1), autosomal recessive disorders (CG, mitochondrial diseases), autoimmune diseases (Addison’s disease), specific single-gene defects (EIF4ENIF1, EIF2B, FOXL2, GDF9, FOXO3, FSHR, etc.), and iatrogenic causes (chemotherapy) (Rossetti et al. 2017). Also, metabolic dysfunction such as obesity is associated with problems in reproduction, including POI (Hohos & Skaznik-Wikiel 2017). While the etiology of POI in all causes is largely unknown, the pathophysiology of POI can be divided into two major categories: developmental problems with primordial follicles resulting in atresia before growth or by follicle depletion through accelerated growth and atresia (Panay et al. 2020).

We can look to other examples of POI caused by damaging environments such as autoimmune, iatrogenic, metabolic syndrome (obesity/high-fat diet), and models of galactose-intoxicated animals to speculate how the follicle damage is caused by abnormal metabolites in CG. Various studies exploring autoimmune causes of POI show that the oocyte, granulosa cells, zona pellucida, steroid hormone-producing cells in developing follicles, and the pituitary–hypothalamic axis can all be a target of harmful antibodies (Forges et al. 2004, Altuntas et al. 2006, Sharif et al. 2019). Induced oophoritis in animal models reveals damage mainly to growing and developing follicles (Domniz & Meirow 2019). Targeted antibody attack of one negative regulator of FSH led to increased FSH and follicle depletion due to increased follicle activation early in life (Altuntas et al. 2006). Chemotherapy agent cyclophosphamide appears to cause POI by damaging DNA, specifically in the primordial oocyte and granulosa cells of developing follicles. The damage to the primordial oocyte leads to a brief moment of growth in the oocyte but then to apoptosis without differentiation to a primary follicle at day one after administration of cyclophosphamide (Luan et al. 2019). There are conflicting interpretations of whether chemotherapy causes primordial follicle death and no increased activation of primordial follicles (Luan et al. 2019) or POI due to increased activation (Kalich-Philosoph et al. 2013); regardless, it is clear that primordial follicle damage contributes to developing POI. Researchers also saw changes in AMH levels after the administration of cyclophosphamide in mice. Three days after administration, AMH fell dramatically, similar to what is seen in humans with follicle damage, and then steadily increased to control levels seven days post-treatment, presumably due to improvement in follicle health after the initial insult (Luan et al. 2019).

Obesity, specifically a high-fat diet, can lead to reproductive dysfunction such as follicular and oocyte damage, lower responses to in vitro fertilization (IVF),
Pathophysiology of primary ovarian insufficiency in galactosemia

The aforementioned models of POI and human examples give clues about what types of insults can cause POI. However, while informative to the development of POI, these models are not specific to CG, as there are presumed normal functions of the GALT enzyme. Indistinct prenatal insults are possible in CG female ovaries due to endogenous production of galactose; however, this has only been examined in galactose-intoxicated rat models of POI and not measured in human fetuses (Bandyopadhyay et al. 2003b). While the exact mechanism of ovarian failure is not known, overwhelming evidence suggests that excess gal-1P is the main culprit in CG POI (Guerrero et al. 2000, Bandyopadhyay et al. 2003a, Tang et al. 2014, Thakur et al. 2017, Vanoevelen et al. 2018, Yuzuk et al. 2018, Balakrishnan et al. 2019). Females heterozygous for pathogenic variants in GALT and with other types of galactosemia, such as GALK1 deficiency, do not have chronically elevated levels of gal-1P, have a normal ovarian reserve, and do not undergo menopause at a premature age (Knauff et al. 2007, Badik et al. 2011, Rubio-Gozalbo et al. 2021). A summary of studies that evaluate the ‘toxic’ action of specific galactose metabolites is presented in Table 2.

The GALT knockout zebrafish and mouse model have the POI phenotype similar to CG humans (Tang et al. 2014, Vanoevelen et al. 2018). Zebrafish with galt-knockout show increased gal-1P, decreased number of eggs after fertilization, and increased galk1 and gale activity in the ovary (Vanoevelen et al. 2018). This model showed aberrant glycosylation and disturbed sialylation in the ovary (Haskovic et al. 2020). Previously, our lab developed a new homozygous GalT-gene trapped mouse model to study the pathophysiology of CG on a multicellular organism (Tang et al. 2014). Galactose sensitivity, reduced fertility in females, hypogalactosylation of IgG, growth restriction, and motor impairment are seen in the GalT-deficient mice in both sexes, similar to humans with CG (Balakrishnan et al. 2016, 2017, Chen et al. 2017).

In our mouse model, we see subfertility, reduced follicles, increased corpus luteum, increased ER/UPR stress markers, and decreased PI3K/AKT signaling in two-month-old ovaries compared to WT ovaries (Balakrishnan et al. 2017, 2019). While there were significantly fewer primordial follicles at two months of age, follicle counts at postnatal day eight (unpublished data) showed no difference in primordial follicles when compared to WT mice, suggesting that follicle loss occurs progressively between birth and sexual maturity in a mouse, similar and problems in the hypothalamic-pituitary-ovarian (HPO) axis likely due to high levels of insulin (Luke et al. 2011, Broughton & Moley 2017, Hohos and Skaznik-Wikel 2017). Limited mechanistic studies of obesity/high-fat diet and the ovary are available in humans beyond association data; however, women fed a high-fat diet for two to four menstrual cycles experienced characteristics of POI such as cycle disruption, a shorter time between menses, increased FSH, and decreased estradiol (Hill et al. 1984, Reichman et al. 1992). Machtinger and colleagues assessed the quality of oocytes from obese women that failed fertilization during IVF and found disruptions in spindle and chromosome alignment (Machtinger et al. 2012). Additionally, women with POI are at a greater risk of developing type 2 diabetes, suggesting a metabolic relationship between the two disorders (Anagnostis et al. 2019). Animal studies have shed more light on the potential mechanism causing the disruptions related to obesity such as oxidative stress, mitochondrial dysfunction, HPO axis disruption, and problems in PI3K/AKT signaling (Wu et al. 2010, 2012, Nteeba et al. 2013). In mouse models of obesity, high-fat diet or genetically obese mice have ovarian aging and evidence of POI. Female mice fed high-fat diets had fewer primordial follicles, increased developing follicles, and more corpus luteum than normal caloric or restricted caloric mice (Wang et al. 2014).

Galactose-intoxicated rat models can give some clues to the toxic effects of galactose on the ovary (Rostami Dovom et al. 2019). Early prenatal administration (before 15 days post-conception) of 35% of calories from galactose to mother rats resulted in decreased primordial follicles, increased apoptosis, and disruption in germ cell formation in the pups, suggesting follicle damage in utero (Bandyopadhyay et al. 2003a,b). Other studies found that prenatal and postnatal administration of high galactose (>30%) caused increased FSH and LH and decreased estradiol, similar to human gonadotrophic presentations in POI (Chen et al. 1981). In these studies, the primary metabolite measured was gal-1P; however, the proximal mechanism that contributes to the follicle demise in these models is unknown (Rostami Dovom et al. 2019). Postnatal exposure to high galactose (40%) after weaning increased galactitol concentrations in the ovary and resulted in impaired folliculogenesis; administration of an aldose reductase inhibitor ameliorated the effects of galactitol toxicity suggesting that galactitol and the oxidative stress it creates when it is reduced are potential contributors to ovarian damage in POI in experimental hypergalactosemia. In this study, gal-1P was not measured.
Primary ovarian insufficiency in galactosemia

Table 2 Evidence for galactosemia metabolite toxic action.

| Species/Aberrant metabolites | Consequences | Mechanism | References |
|-----------------------------|--------------|-----------|------------|
| Humans                      |              |           |            |
| Gal-1P                      | Increased risk of long-term complications in humans | Unknown | Yuzyuk et al. (2018) |
| Gal-1P                      | Increased risk of POI in humans | Unknown | Guerrero et al. (2000) |
| Gal-1P                      | Best predictor for verbal dyspraxia | Unknown | Webb et al. (2003) |
| Gal-1P                      | Inhibits growth in fibroblasts derived from galactosemic patients | UDP-hexose deficiency | Lai et al. (2003) |
| Gal-1P                      | Increased stress in GALT negative human-derived fibroblasts | Accumulation of unfolded proteins, altered calcium homeostasis, and ER stress | Slepak et al. (2007) |
| Mouse                       |              |           |            |
| D-galactose, Gal-1P         | Damages MII mouse oocytes and hinders embryo development | Increased ROS and disruption of spindle structure and chromosomal alignment | Thakur et al. (2017) |
| Galactose                   | Decreased oocyte number in offspring | Unknown | Chen et al. (1981) |
| Gal-1P                      | Subfertility, follicular dysfunction, and growth restriction in GALT-deficient mouse models | Unknown | Tang et al. (2014) |
| Gal-1P                      | Reduced growth of mutant mouse fibroblasts | Increased ER stress in mouse fibroblasts via regulation of PI3K/Akt signaling | Balakrishnan et al. (2016) |
| Gal-1P                      | Ovarian dysfunction in galactosemia mouse model | Increased ER stress via regulation of PI3K/Akt signaling | Balakrishnan et al. (2019) |
| Gal-1P                      | Increased ataxia in galactosemia mouse model | Stress-related cellular damage via regulation of PI3K/Akt signaling | Chen et al. (2017) |
| Galactose, galactitol, Gal-1P| Follicular atresia | Unknown | Bandyopadhyay et al. (2003a) |
| Galactose                   | Adverse germ cell migration with initial low pool of germ cells | Unknown | Bandyopadhyay et al. (2003b) |
| Galactitol Yeast            | Cataracts | Unknown | Ai et al. (2000) |
| Gal-1P                      | Growth arrest in yeast models | Increased environmental stress | Slepak et al. (2005) |
| Gal-1P                      | Growth arrest in galactosemia yeast models | Unknown | Ross et al. (2004) |
| Gal-1P                      | Decreased growth rate in yeast | Decrease in intracellular phosphate levels | Machado et al. (2017) |
| Gal-1P                      | Growth arrest of GALT negative yeast | Unknown | Mumma et al. (2008) |
| Gal-1P                      | Decreased growth rates in galactosemic yeast model | Inhibition of phosphoglucomutase | de Jongh et al. (2008) |
| Zebrafish                   | Reduction in motor function and fertility potential | unknown | Vanoevelen et al. (2018) |

to case reports in females with CG (Kaufman et al. 1981, Balakrishnan et al. 2019). Recently, we used Salubrinal to modulate the UPR signaling in our GALT-deficient mouse model (Balakrishnan et al. 2019). Salubrinal inhibits the dephosphorylation of EIF2A, keeping protein translation reduced in the cell. The administration of Salubrinal at five weeks of life improved the fertility of GALT-deficient female mice by normalizing estrus cycles and increasing the number of pups born per litter (Balakrishnan et al. 2019). Histologic analysis of ovaries from Salubrinal-treated mice showed an increased number of primordial follicles when compared to untreated GALT-deficient mice (Balakrishnan et al. 2019).

It is reasonable to assume that the administration of Salubrinal, which allows for increased pEIF2A, may help to keep primordial follicles quiescent, and thus, preserve ovarian function. However, it is unknown if ovarian failure in CG is due to premature activation of primordial follicles or follicle atresia before activation. Preliminary data from our lab comparing one-month-old ovaries showed an
increased ratio of primary to primordial follicles in GALT-deficient mice suggesting premature follicle activation and thus, depletion before sexual maturity (unpublished data). Immunofluorescent histological studies show evidence of increased ER stress marker BiP at two weeks of life in the granulosa cells of follicles in GALT-deficient ovaries (unpublished data).

Our lab found decreased markers of PI3K/AKT signaling in GALT-deficient fibroblasts and whole ovaries at two months of age compared to age-matched WT mice (Balakrishnan et al. 2016, 2017). The ovarian histology revealed a significant decrease in ovarian follicles of all stages and increased corpus luteum tissue (Balakrishnan et al. 2017). Interestingly, after administration of Salubrinal to GALT-deficient mice, molecular markers of PI3K/AKT signaling were improved in the whole ovary as well as an increased number of follicles (Balakrishnan et al. 2019). The relationship between the UPR and PI3K/AKT signaling is not well understood, but it appears that there is a communication between the phosphorylation of EIF2A and the phosphorylation of AKT (Qin et al. 2010, Tian et al. 2011). As PI3K/AKT signaling is tightly regulated in follicle activation, we speculate that by keeping EIF2A phosphorylated, proper signaling is restored in the primordial follicle, allowing for follicle quiescence. Differences in PI3K/AKT signaling at earlier ages have not been explored in our mouse model of CG or the specific cell types involved. If there is evidence of early, mass primordial follicle activation in GALT-deficient mice, immunofluorescent studies may reveal increased PI3K/AKT signaling in oocytes/granulosa cells at earlier time points in development (Jagarlamudi et al. 2009). Modulators of PI3K/AKT signaling could also be used as a potential treatment if indicated, once the pathophysiology of POI in galactosemia is elucidated.

**Clinical considerations**

**Evaluation of POI in galactosemia**

The clinical presentation for CG-induced POI can manifest as delayed or absent puberty, primary or secondary amenorrhea, oligomenorrhea, or infertility (Fridovich-Keil et al. 2011, Thakur et al. 2018). In 2017, members of The Galactosemia Network (GalNet) developed evidence-based guidelines for the diagnosis, treatment, and follow-up of CG including specific recommendations related to endocrinology and fertility (Welling et al. 2017). The guidelines recommend that all females with CG be screened for POI by the age of 12 with absent secondary sexual characteristics or if they reach age 14 with irregular menses, and screening should include serum FSH and estradiol measurements. Additionally, the guidelines also recommend that females with CG that have undergone puberty with regular ongoing menstrual periods be monitored annually for signs or symptoms of POI and FSH measurement if symptoms arise (Welling et al. 2017). We provide a summary of guidelines for clinical management specific to CG and more broadly to POI in Table 3.

Alternative methods for screening for POI have been evaluated including measuring AMH levels. AMH is produced by granulosa cells of pre-antral and antral follicles, and its use has become more widespread in measuring ovarian reserve (Hagen et al. 2010, Hansen et al. 2011). While the guidelines currently recommend against using AMH as a screening tool for POI in this patient population (Welling et al. 2017), there have been several studies that have evaluated AMH levels in CG-induced POI (Spencer et al. 2013, Frederick et al. 2018). Studies show that patients with CG have significantly lower AMH values than controls, and AMH values can be assessed before menarche or after initiation of HRT (Sanders et al. 2009, Spencer et al. 2013) supporting its potential utility for screening. More recently, Frederick and colleagues (Frederick et al. 2018) measured both AMH and FSH in patients with CG and tested for possible association(s) with spontaneous menarche. They found that a detectable AMH level (≥0.04 ng/mL) was highly predictive of spontaneous menarche. FSH values, unlike AMH, did not associate with spontaneous menarche. AMH values are also useful in screening for POI in patients with Turner syndrome (Hagen et al. 2010, Lunding et al. 2015). In prepubertal patients, an AMH less than 0.56 ng/mL predicted the absence of puberty in Turner syndrome girls (Lunding et al. 2015). With recent advances in AMH assay sensitivity as well as evidence of its utility in predicting menarche, we recommend routinely checking AMH levels in prepubertal patients with CG and those that have not been diagnosed with POI.

**Management of POI in galactosemia**

In CG patients with primary amenorrhea and absent puberty, the GalNet guidelines recommend starting with low-dose estradiol and increasing the dosage in a step-wise fashion to mimic physiological ovarian hormone function, with progesterone supplementation at a later time to induce withdrawal bleeding for endometrial protection (Welling et al. 2017). The exact timing of when to start HRT for young girls with CG and POI has not been well...
Table 3  Clinical management of galactosemia and POI.

| Age   | Guidelines                                                                 | Unknows                                                                 | Considerations                                                                 | Supporting references                                                                 |
|-------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Newborn | 1. Screening for galactosemia                                              | 1. Utility of monitoring ovarian reserve to evaluate for imminent POI  | 1. Draw FSH and AMH annually                                                  | (Mamsen et al. 2018, Frederick et al. 2018, Yuzyk et al. 2018, Azem et al. 2020, Poiriot et al. 2019, Segers et al. 2020, Sanders et al. 2009) |
|       | 2. Implementing dietary management                                         | 2. Age to consider fertility preservation                               | 2. Consider fertility preservation options (OTC vs oocyte cryopreservation) under research protocol as follicular numbers appear to be normal in younger patients |                                                                                       |
| 1–11 years | 1. Monitor Gal-1P levels regularly to ensure dietary compliance            | 3. The role ER stress blockers play in maintaining fertility potential   | 3. Is there a role for routine fertility preservation in this age group       | (Mamsen et al. 2018, Frederick et al. 2018, Cobo et al. 2016, Poiriot et al. 2019, Segers et al. 2020) |
|       |                                                                          | 1. Is there a role for routine fertility preservation for patients with adequate ovarian reserve | 1. Recommend adding AMH to screening protocol for POI as it appears to be predictive of spontaneous menarche |                                                                                       |
| 12–14 years | 1. Monitor secondary sexual characteristics and menarche                  | 2. The role ER stress blockers play in maintaining fertility potential   | 2. Consider fertility preservation in patients with evidence of adequate ovarian reserve |                                                                                       |
|       | 2. Screen for POI (FSH, E2) if no secondary sexual characteristics by age 12 or irregular menses by age 14 |                                                                          | 1. Include AMH as routine screening for POI                                   | (Mamsen et al. 2018, Frederick et al. 2018, Yuzyk et al. 2018, Cobo et al. 2016, Poiriot et al. 2019, Segers et al. 2020) |
|       | 3. Initiate HRT if POI diagnosed                                           |                                                                          | 2. Consider fertility preservation (OTC vs oocyte cryopreservation) in patients with evidence of adequate ovarian reserve |                                                                                       |
| 14+ years | 1. Monitor annually for menstrual changes and symptoms of POI in women who underwent puberty. Screen for POI with concerns (FSH) |                                                                          | 1. Draw FSH and AMH annually                                                  | (Mamsen et al. 2018, Frederick et al. 2018, Yuzyk et al. 2018, Cobo et al. 2016, Poiriot et al. 2019, Segers et al. 2020) |
|       | 2. Initiate HRT for newly diagnosed POI                                   |                                                                          | 2. Consider fertility preservation options (OTC vs oocyte cryopreservation) under research protocol as follicular numbers appear to be normal in younger patients |                                                                                       |
|       | 3. Counsel on spontaneous conception and implement contraception if needed |                                                                          | 3. Is there a role for routine fertility preservation for patients with adequate ovarian reserve |                                                                                       |
|       | 4. Refer to REI for fertility considerations                               |                                                                          | 1. Recommend adding AMH to screening protocol for POI as it appears to be predictive of spontaneous menarche |                                                                                       |
|       | 5. Screen for emotional well-being                                        |                                                                          | 2. Consider fertility preservation in patients with evidence of adequate ovarian reserve |                                                                                       |

established but is generally started once the patient is at a peri-pubertal age, and the diagnosis of POI has been made.

According to the ESHRE guidelines on POI in the general population, low-dose estradiol should be started between ages 12–13 if no secondary sexual characteristics are present, and FSH is elevated. Estradiol should be gradually increased every 6–12 months for 2–3 years until an adult dosage is reached, and cyclic progesterone should be started after two years of estradiol or with the onset of breakthrough bleeding (Webber et al. 2016). There are many different routes of estrogen replacement including oral, transdermal, and transvaginal (Sullivan et al. 2016) with no form showing superiority in regards to improvement in symptoms (Webber et al. 2017); however, transdermal and transvaginal routes showed decreased occurrence of venous-thromboembolism (VTE) in postmenopausal patients, but this has not been shown in younger populations (Webber et al. 2017, Vinogradova et al. 2019). However, given the duration of therapy in this population and the paucity of long-term longitudinal studies in pre-menopausal women with POI, mitigating VTE risk with transdermal and transvaginal administration may be prudent (Canonico et al. 2014).

Progesterone supplementation is traditionally given orally in either a micronized progesterone form or as a synthetic progestogen such as medroxyprogesterone acetate in a cyclical manner to induce regular menstrual cycles; it also can be given continuously in patients that do not desire a menstrual cycle. Alternative forms of progesterone are available such as transdermal, transvaginal, and intrauterine including the levonorgestrel intrauterine device (LNG-IUD) which supplies endometrial
protection while also allowing for contraception (Webber et al. 2017). Some patients may prefer combined oral contraceptive pills (COCPs) as an alternative to traditional HRT as this is often more socially acceptable in their age group. However, studies have suggested that COCPs are inferior to HRT in maintaining bone health, but sample sizes have been small (Crofton et al. 2010, Cartwright et al. 2016). Patients who elect COCP use for HRT long-term should also be advised of the lack of improvement in associated genitourinary symptoms with this formulation compared to 17-beta estradiol as well as the lack of potential cardiovascular protection. Patients with CG should be counseled to take the COCP continuously and skip the placebo pills which would render them without estrogen or progesterone for 25% of the time (Webber et al. 2017). Finally, individuals should be counseled that HRT is not a form of contraception, and if pregnancy is not desired, a form of contraception should be recommended.

Psychosocial parameters including social well-being and social functioning are lower in patients with CG compared to the general population (Hoffmann et al. 2012). These patients are also prone to anxiety and depression with one observational study showing 67% of CG subjects reporting anxiety and 39% reporting depression (Waisbren et al. 2012). Also, decreased emotional well-being, anxiety, and depression are also significant factors associated with POI (Nelson 2009). Young women diagnosed with ‘early menopause’ may feel stigmatized and often devastated at the diagnosis especially when understanding the current incurable nature of the disease, related infertility, and being different than their peers (Sterling & Nelson 2011). A cross-sectional and case-control study by Davis and colleagues comparing spontaneous conception in women with 46,XX with a mean age of 32.4 years to age-matched controls found that those with POI had increased anxiety, depression, and negative affect as well as decreased overall well-being (Davis et al. 2010). Patients also perceive a lack of psychosocial support after receiving the diagnosis of POI, and few receive appropriate follow-up from social workers or a psychologist (Kanj et al. 2018). Appropriate counseling regarding the diagnosis as well as psychological support is extremely important in this patient population, and perhaps a multidisciplinary team approach is the best management method.

Fertility management

Infertility is a major long-term effect in patients with POI, although there are reports of spontaneous pregnancy in this population. The ovarian function in these women is limited, but erratic and unpredictable ovulation can still occur. In the broader POI population, 5–10% spontaneously conceive (van Kasteren & Schoemaker 1999). As mentioned previously, patients with CG continue to have ovarian compromise despite being on a galactose-restricted diet and many eventually experience POI. Yet, recent data has suggested fertility rates are higher in those patients with CG-induced POI compared to other causes of POI. In a study of 22 CG women, nine attempted to conceive spontaneously and four were successful (44% pregnancy rate) (Gubbels et al. 2008). Similar findings were detected in a recent observational study that evaluated 85 women with CG. In those patients, 21 actively attempted to conceive and nine achieved pregnancy (42.9% pregnancy rate) (van Erven et al. 2017). Even in CG patients with undetectable AMH levels and menopausal FSH levels, pregnancy can be achieved (Gubbels et al. 2009) (see as an example, Table 1). Ovarian reserve markers like FSH, AMH, and antral follicle count can help predict ovarian reserve and fertility potential but are not definitive in determining which patients with POI will and will not conceive. It is important to counsel patients appropriately on the chance of spontaneous conception and despite the diagnosis of POI, and for patients that do not desire pregnancy, contraception is recommended (Welling et al. 2017).

For those patients that do not achieve spontaneous conception and desire to conceive, referral to a reproductive endocrinologist to discuss fertility options such as oocyte and embryo donation should occur with adoption also being an alternative option (Baker 2011). Patients with POI are generally not ideal candidates to undergo IVF using autologous oocytes due to the extremely low chances of success secondary to depleted follicular reserve; while oocyte donation from a donor < 35 years of age would yield a live birth rate of approximately 44% (Hogan et al. 2019). Maintaining uterine health with estradiol and progesterone replacement therapy is thus important in helping these women achieve their family building goals.

Fertility preservation

Fertility preservation options are studied more in patients undergoing gonadotoxic therapy such as chemotherapy for cancer treatment that would render them at high risk for ovarian insufficiency and infertility, but it should also be offered to people with more benign conditions that put them at high risk for ovarian insufficiency (Donnez & Dolmans 2017). Historically, the two standard methods for fertility preservation have been oocyte cryopreservation...
and embryo cryopreservation which have been utilized for over 30 years. With either method, the patient receives exogenous gonadotropins for ovarian stimulation, and the resulting growing ovarian follicles are then aspirated to retrieve the oocytes. The oocytes can either be frozen to be used for embryo creation at a later date, or the fresh oocytes can be fertilized with partner or donor sperm after the retrieval to create embryos. The resulting embryos are grown to the blastocyst stage and are frozen to be thawed and transferred at a later date. In patients with a good prognosis (i.e. 35 years of age or younger), 10 oocytes cryopreserved yield a cumulative live birth rate of 60.5%, and 15 oocytes yield a cumulative live birth rate of 85.2% (Cobo et al. 2016). Unfortunately, due to the rapid depletion of the ovarian reserve pool often before puberty in patients with CG, oocyte and embryo cryopreservation are generally not a practical option for fertility preservation in this population. To date, there are no studies evaluating the utility of oocyte cryopreservation in post-puberal patients with CG that have retained ovarian function. Due to the immaturity of the HPO axis in prepubertal girls, exogenous stimulation with gonadotropins for oocyte cryopreservation has historically not been viewed as a viable option, but a recent publication has challenged this approach. Azem and colleagues report the case of a seven-year-old female with Turner syndrome mosaicism that underwent controlled ovarian hyperstimulation with six mature oocytes cryopreserved (Azem et al. 2020). Successful oocyte cryopreservation in a prepubertal patient at high risk for developing POI is an exciting potential option for patients with CG but will require further studies. Considerations include patient maturity to undergo stimulation at this age as well as utilization of transvaginal ultrasound for follicular monitoring with transvaginal retrieval under anesthesia.

OTC, which requires surgical removal of ovarian tissue cortex that is subsequently frozen and re-implanted at a later date, is becoming a more widespread and promising option that has also resulted in > 130 live births (Donnez & Dolmans 2017, Gellert et al. 2018). Recently, ASRM lifted the experimental label for OTC that can now be offered as a standard of care (Medicine ECotASfR 2018). Traditionally in prepubertal females, OTC has been seen as the only option for fertility preservation which was generally completed under a research protocol (Medicine ECotASfR 2018, Nahata et al. 2020). Currently, there is limited evidence regarding the safety and effectiveness of OTC in prepubertal patients with only one live birth as a result of OTC from a prepubertal patient (Matthews et al. 2018). However, there have been several reports of successful induction of puberty with tissue harvested from prepubertal girls, cryopreserved, and transplanted in early adolescence supporting the efficacy of prepubertal OTC (Ernst et al. 2013, Poirot et al. 2019). Regarding CG, there are no data concerning OTC in postpubertal patients, but recent data show a potential benefit for OTC in pre-pubertal patients with CG. Six girls with galactosemia below the age of 12 underwent OTC for fertility preservation. Normal ovarian follicular density and morphology were observed in five of the girls (all ages 5 or younger) compared to controls that underwent OTC before receiving gonadotoxic therapy. The remaining girl with CG that underwent OTC was 11.7 years, and there were no ovarian follicles detected (Mamsen et al. 2018).

In vitro maturation (IVM) is the process of maturing cumulus-oocyte complexes (COCs) to the metaphase II stage in a culture which can then be used for embryo creation or oocyte cryopreservation. Improvements in lab techniques have resulted in significant improvement in IVM success. A recent retrospective study included 77 patients who underwent OTC with the maturation of COCs obtained during ovarian tissue processing. IVM rate of immature oocytes to the metaphase II stage was 39%. Of the 77 patients, 64 had oocytes cryopreserved, and the live birth rate per patient that underwent ovarian tissue oocyte IVM followed by fertilization and embryo transfer was 43% (Segers et al. 2020).

Overall, there is a lack of evidence of the utility of fertility preservation in patients with non-oncologic causes of POI specifically in the prepubertal population. In particular, in patients with CG-induced POI, there is concern that the ovarian damage might have already occurred yielding OTC futile, and this process of removing ovarian tissue will further decrease the ovarian reserve in a population that is at high risk for POI with spontaneous conception still being possible (van Erven et al. 2013). Partial oophorectomy for OTC may be considered to allow retention of tissue in the event of spontaneous ovulation and conception. Currently, the guidelines do not recommend for patients with CG to undergo routine fertility preservation techniques, and these procedures should only be offered under research studies at young prepubertal ages (van Erven et al. 2013, Welling et al. 2017). Given the recent studies, albeit limited numbers, it appears young prepubertal girls less than five years of age with CG have normal ovarian follicular numbers and morphology. These findings coupled with the advancements in OTC and IVM show this as a promising method for fertility preservation in this patient population. Further studies need to be completed, but it is reasonable to discuss this
option with patients and refer them to specialized centers as needed.

**Limitations and future directions**

There are limitations to our review, including the lack of fertility preservation data on postpubertal patients with CG. Due to the high prevalence of early-onset POI, there are no studies evaluating fertility preservation in this age group. The considerations for fertility preservation in this population are extrapolated from the successes in similar patients with adequate ovarian reserve, which may influence clinical recommendations. The ER stress modulator Salubrinal is for research only and not safe for human use. Additionally, no data exists using ER stress modulators in human models of POI, making this target difficult to translate to a clinical setting. Finding FDA-approved drugs or nutraceuticals with similar mechanisms of action could be considered. Finally, the review of human and animal models of POI presented here are not specific to GALT deficiency, and the mechanisms that cause POI in the other models may not apply to CG. The mechanism of follicle demise may be very specific to the metabolites and cellular metabolism present in CG.

After over 50 years of research, the true pathophysiology of galactosemia remains unclear (Rubio-Gozalbo et al. 2019). No treatments for POI in galactosemia or the general population are used except for HRT, which only counters the effects of early menopause and does not prevent ovarian failure (Hadjı 2008). Currently, gene/mRNA therapies and GALK1 inhibitors are being developed to treat GALT deficiency (Lai et al. 2014, Hu et al. 2019, Balakrishnan et al. 2020). However, it may be several years before this is available to human patients. Inhibitors of aldose reductase (AR), the enzyme responsible for converting excess galactose to galactitol, are also being explored as a potential treatment for galactosemia. AR inhibitors have the potential to be effective in protecting the ovary in particular from oxidative stress, which has been studied in a galactose-intoxicated rat model, but its relevance in patients with a galactose-restricted diet remains to be seen (Meyer et al. 1992). While Salubrinal showed improved fertility and increased primordial follicles in GALT-deficient mice (Kobayashi et al. 1999), its safety in humans is not well studied. At this time, compounds with a similar mechanism of action to Salubrinal and specific dietary supplements that are either FDA-approved or generally recognized as safe (GRAS) in humans are being tested as a treatment for POI in galactosemia. If a potential therapy is found, the timing of treatment for females with galactosemia remains to be determined.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

**Funding**

This work was supported the National Institutes of Health (grant number R01HD088993, PI: Lai), and by University of Colorado School of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, and Florence Crozier Cobb Research Funds (to J J). McPherson Family Funds are also gratefully acknowledged.

**Author contribution statement**

J J and K L conceived of the manuscript, contributed to its writing, and supervised revisions. S H-L and J R wrote and revised manuscript drafts, collected data, and summarized literature for tables. A A collected data and reviewed manuscript, L A and N L contributed to manuscript content and provided clinical context.

**Acknowledgements**

De-identified patient data are reported under the auspices of approved University of Utah protocol IRB_00085855 – Natural history of patients with metabolic disorders.

**References**

Adhikari D & Liu K 2009 Molecular mechanisms underlying the activation of mammalian primordial follicles. Endocrine Reviews 30: 438–464. (https://doi.org/10.1210/er.2008-0048)

Adhikari D, Zheng W, Shen Y, Gorre N, Hämäläinen T, Cooney AJ, Huhtaniemi I, Lan ZJ & Liu K 2010 Tsc/mTORC1 signaling in oocytes governs the quiescence and activation of primordial follicles. Human Molecular Genetics 19: 397–410. (https://doi.org/10.1093/hmg/ddp483)

Ai Y, Zheng Z, O’Brien-Jenkins A, Bernard DJ, Wynshaw-Boris T, Ning C, Reynolds R, Segal S, Huang K & Stambolian D 2000 A mouse model of galactose-induced cataracts. Human Molecular Genetics 9: 1821–1827. (https://doi.org/10.1093/hmg/9.12.1821)

Altuntas CZ, Johnson JM & Tuohy VK 2006 Autoimmune targeted disruption of the pituitary-ovarian axis causes premature ovarian failure. Journal of Immunology 177: 1988–1996. (https://doi.org/10.4049/jimmunol.177.3.1988)

Alves VS, Motta FL, Roffe M, Delamano A, Pesquero JB & Castilho BA 2009 GCN2 activation and elf2alpha phosphorylation in the maturation of mouse oocytes. Biochemical and Biophysical Research Communications 378: 41–44. (https://doi.org/10.1016/j.bbrc.2008.10.161)

Anagnostis P, Christou K, Artzouchaltzi AM, Gkekas NK, Kosmidou N, Siolos P, Paschou SA, Potoupinis M, Kenanidis E, ...
S Hagen-Lillevik, J S Rushing et al.
Primary ovarian insufficiency in galactosemia

Primary ovarian insufficiency is associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. European Journal of Endocrinology 180 41–50. (https://doi.org/10.1530/EJE-18-00602)

Antshel KM, Epstein IO & Waisbren SE 2004 Cognitive strengths and weaknesses in children and adolescents homozygous for the galactosemia Q188R mutation: a descriptive study. Neuropsychology 18 658–664. (https://doi.org/10.1037/0894-4105.18.4.658)

Azem F, Brener A, Malinger A, Reches A, Many A, Yoge V & Lebenthal Y 2020 Bypassing physiological puberty, a novel procedure of oocyte cryopreservation at age 7: a case report and review of the literature. Fertility and Sterility 114 374–378. (https://doi.org/10.1016/j.fertnstert.2020.03.009)

Babayev E, Lalioti MD, Favero F & Selin E 2016 Cross-talk Between FSH and endoplasmic reticulum stress: a mutually suppressive relationship. Reproductive Sciences 23 352–364. (https://doi.org/10.1177/1933719115602270)

Badlik JB, Castañeda U, Gleason TJ, Spencer JB, Epstein MP, Ficicioglu C, Fitzgerald K & Fridovich-Keil JL 2011 Ovarian function in Duarte galactosemia. Fertility and Sterility 96 469 e461–473. (https://doi.org/10.1016/j.fertnstert.2011.05.088)

Baker V 2011 Life plans and family-building options for women with primary ovarian insufficiency. Seminars in Reproductive Medicine 29 362–372. (https://doi.org/10.1055/s-0031-1280921)

Balakrishnan B, Chen W, Tang M, Huang X, Cakici DD, Siddiqi A, Berry G & Lai K 2016 Galactose-1-phosphate uridylyltransferase (GALT) gene: a novel positive regulator of the PI3K/Akt signaling pathway in mouse fibroblasts. Biochemical and Biophysical Research Communications 470 205–212. (https://doi.org/10.1016/j.bbrc.2016.01.036)

Balakrishnan B, Nicholas C, Siddiqi A, Chen W, Bales E, Feng M, Johnson J & Lai K 2017 Reversal of aberrant PI3K/Akt signaling by Salubrinal in a GALT-deficient mouse model. Biochemistry and Biophysical Acta: Molecular Basis of Disease 1863 3286–3293. (https://doi.org/10.1016/j.bbadis.2017.08.023)

Balakrishnan B, Siddiqi A, Mella J, Lupo A, Li E, Hollien J, Johnson J & Lai K 2019 Salubrinal enhances eIF2α phosphorylation and improves fertility in a mouse model of classic galactosemia. Biochimica et Biophysica Acta: Molecular Basis of Disease 1865 165316. (https://doi.org/10.1016/j.bbadis.2019.07.010)

Balakrishnan B, An D, Nguyen V, DeAntonis C, Martini PGV & Lai K 2020 m7Gcap mRNA-based therapy reduces toxic galactose metabolites and overcomes galactose sensitivity in a mouse model of classic galactosemia. Molecular Therapy 28 304–312. (https://doi.org/10.1038/s41392-019-0303-1)

Bandyopadhyay S, Chakrabarti J, Banerjee S, Pal AK, Goswami SK, Chakravarty BN & Kabir SN 2003a Galactose toxicity in the rat as a model for premature ovarian failure: an experimental approach readressed. Human Reproduction 18 2031–2038. (https://doi.org/10.1093/humrep/deg414)

Bandyopadhyay S, Chakrabarti J, Banerjee S, Pal AK, Bhattacharyya D, Goswami SK, Chakravarty BN & Kabir SN 2003b Prenatal exposure to high galactose adversely affects initial gonadal pool of germ cells in rats. Human Reproduction 18 276–282. (https://doi.org/10.1093/humrep/deg058)

Batey LA, Welt CK, Rohr F, Wessel A, Anastassoaei V, Feldman HA, Guo CY, Rubio-Gozalbo E, Berry G & Gordon CM 2013 Skeletal health in adult patients with classic galactosemia. Osteoporosis International 24 501–509. (https://doi.org/10.1007/s00198-012-2193-0)

Berry GT 2020 Cross galactosemia and clinical variant galactosemia. In Genelreviews® Available at https://www.ncbi.nlm.nih.gov/books/NBK1358/ (Accessed: 10 September 2020).

Berry GT, Nissim I, Gibson JB, Mazur AT, Lin Z, Elassa LJ, Singh RH, Klein PD & Segal S 1997 Quantitative assessment of whole body galactose metabolism in galactosemic patients. European Journal of Pediatrics 156 (Supplement 1) S43–S49. (https://doi.org/10.1007/pI00004271)

Berry GT, Moate PJ, Reynolds RA, Yager CT, Ning C, Boston RC & Segal S 2004 The rate of de novo galactose synthesis in patients with galactose-1-phosphate uridylyltransferase deficiency. Molecular Genetics and Metabolism 81 22–30. (https://doi.org/10.1016/j.mgme.2003.08.026)

Broughton DE & Moley KH 2017 Obesity and female infertility: potential mediators of obesity’s impact. Fertility and Sterility 107 840–847. (https://doi.org/10.1016/j.fertnstert.2017.01.017)

Canonicom M, Plu-Bureau G, O’Sullivan MJ, Stefanick ML, Cochrane B, Scarabini PY & Mannon JE 2014 Age at menopause, reproductive history, and venous thromboembolism risk among postmenopausal women: the Women’s Health Initiative Hormone Therapy clinical trials. Menopause 21 214–220. (https://doi.org/10.1097/GME.00001382189720)

Cartwright B, Robinson J, Seed PT, Fogelman & Rymer J 2016 Hormone replacement therapy versus the combined oral contraceptive pill in premature ovarian failure: a randomized controlled trial of the effects on bone mineral density. Journal of Clinical Endocrinology and Metabolism 101 3497–3505. (https://doi.org/10.1210/jc.2015-4063)

Chakravarthi VP, Ghosh S, Roby KF, Wolfe MW & Rumi MAK 2020 A gatekeeping role of ESRR2 to maintain the primordial follicle reserve. Endocrinology 161. (https://doi.org/10.1201/endocr/bqaa037)

Chang HM, Qiao J & Leung PC 2016 Oocyte- somatic cell interactions in the human ovary–novel role of bone morphogenetic proteins and growth differentiation factors. Human Reproduction Update 23 1–18. (https://doi.org/10.1093/humupd/dmw039)

Chen VT, Mattison DR, Feigenbaum L, Fukui H & Schulman JD 1981 Reduction in oocyte number following prenatal exposure to a diet high in galactose. Science 214 1145–1147. (https://doi.org/10.1126/science.7302587)

Chen W, Castor R, Balakrishnan B, Siddiqi A, Parmar K, Tang M, Feng M & Lai K 2017 Assessment of ataxia phenotype in a new mouse model of galactose-1-phosphate uridylyltransferase (GALT) deficiency. Journal of Inherited Metabolic Disease 40 131–137. (https://doi.org/10.1055/s-0035-1599993)

Cobo A, García-Velasco JA, Coello A, Domingo J, Pellicer A & Remohi J 2016 Oocyte vitrification as an efficient option for elective fertility preservation. Fertility and Sterility 105 755.e8–764.e8. (https://doi.org/10.1016/j.fertnstert.2015.11.027)

Colegrove-Otero LJ, Minshall N & Standart N 2005 RNA-binding proteins in early development. Critical Reviews in Biochemistry and Molecular Biology 40 21–73. (https://doi.org/10.1080/10492350590186121)

Crofton PM, Evans N, Bath LE, Warner P, Whitehead TJ, Critchley HO, Kelner CJ & Wallace WHB 2010 Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover. Clinical Endocrinology 73 707–714. (https://doi.org/10.1111/j.1365-2265.2010.03868.x)

Davis M, Ventura J, Wieneres M, Covingtnon SN, Vanderhoof VH, Ryan ME, Koziol DE, Popat VB & Nelson LM 2010 The psychosocial transition associated with spontaneous 46, XX primary ovarian insufficiency: illness uncertainty, stigma, goal flexibility, and purpose in life as factors in emotional health. Fertility and Sterility 93 2321–2329. (https://doi.org/10.1016/j.fertnstert.2008.12.122)

de Jongh WA, Bro C, Ostgaard S, Regenberg B, Olsson L & Nielsen J 2008 The roles of galactitol, galactose-1-phosphate, and phosphoglucomutase in galactose-induced toxicity in Saccharomyces cerevisiae. Biotechnology and Bioengineering 101 317–326. (https://doi.org/10.1002/bit.21890)

Dorniz N & Meliow D 2019 Premature ovarian insufficiency and autoimmune diseases. Best Practice and Research: Clinical
Kaufman FR, Kogut MD, Donnelly GN, Goebelsmann U, March C & Koch R 1981 Hypergonadotrop hypergonadism in female patients with galactosemia. New England Journal of Medicine 304 994–998. (https://doi.org/10.1056/NEJM198104233304170)

Kawamura K, Cheng Y, Suzuki N, Deguchi M, Sato Y, Takae S, Ho CH, Kawamura N, Tamura M, Hashimoto S, et al. 2013 Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. PNAS 110:1747–17479. (https://doi.org/10.1073/pnas.1312830110)

Knauff EA, Richardus R, Eijkemans MJ, Broekmans FJ, de Jong FJ, Fauser BC & Bosch AM 2007 Heterozygosity for the classical galactosemia mutation does not affect ovarian reserve and menopausal age. Reproductive Sciences 14 780–785. (https://doi.org/10.11719/rrs19170308614)

Kobayashi K, Sinasac DS, Lijima M, Boright AP, Begum L, Lee JR, Yasuda T, Ikeda S, Hirano R, Terazono H, et al. 1999 The gene mutated in adult-onset type II citrullinemia encodes a putative mitochondrial carrier protein. Nature Genetics 22 159–163. (https://doi.org/10.1038/ng5667)

Komatsu K & Masubuchi S 2017 The concentration-dependent effect of progesterone on follicle growth in the mouse ovary. Journal of Reproduction and Development 63 271–277. (https://doi.org/10.1262/jrd.2016-154)

Kumar SU, Kumar DT, Siva R, Doss CGP & Zayed H 2014 GALK inhibitors for classic galactosemia. Future Medicinal Chemistry 6 1003–1015. (https://doi.org/10.4155/fmc.14.43)

Le Bouffant R, Boulben S, Cormier P, Mulner-Lorillon O, Bellé R, Lai K, Boxer MB & Marabotti A 2014 GALK inhibitors for classic galactosemia. Future Medicinal Chemistry 6 1003–1015. (https://doi.org/10.4155/fmc.14.43)

Kumar SU, Kumar DT, Siva R, Doss CGP & Zayed H 2020 An extensive computational approach to analyze and characterize the functional mutations in the galactose-1-phosphate uridyl transferase (GALT) protein responsible for classical galactosemia. Computers in Biology and Medicine 117 103583. (https://doi.org/10.1016/j.compbiomed.2019.103583)

Kai K, Langley SD, Kihwa FW, Schmitt EW & Elsas LJ 2003 GALT deficiency causes UDP-hexose deficit in human galactosemic cells. Glycobiology 13 285–294. (https://doi.org/10.1093/glycob/cwg033)

Kai K, Boxer MB & Marabotti A 2014 GALK inhibitors for classic galactosemia. Future Medicinal Chemistry 6 1003–1015. (https://doi.org/10.4155/fmc.14.43)

Lin P, Yang Y, Li X, Chen F, Cui C, Hu L, Li Q, Liu W & Jin Y 2012 Endoplasmic reticulum stress is involved in granulosa cell apoptosis during follicular atresia in goat ovaries. Molecular Reproduction and Development 79 423–432. (https://doi.org/10.1002/mrd.22045)

Liu K, Rajareddy S, Liu L, Jagarlamudi K, Boman K, Selstam G & Reddy PP 2006 Control of mammalian oocyte growth and early follicular development by the oocyte PI3 kinase pathway: new roles for an old timer. Developmental Biology 299 1–11. (https://doi.org/10.1016/j.ydbio.2006.07.038)

Luan Y, Edmonds ME, Woodruff TK & Kim SY 2019 Inhibitors of apoptosis protect the ovarian reserve from cyclophosphamide. Journal of Endocrinology 240 243–256. (https://doi.org/10.1633/JOE-18-0370)

Luke B, Brown MB, Stern JE, Misser SA, Fujimoto VY, Leach R & SART Writing Group 2011 Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Human Reproduction 26 245–252. (https://doi.org/10.1093/humrep/dec036)

Lunding SA, Aksgäide I, Anderson RA, Main KM, Juul A, Hagen CP & Pedersen AT 2015 AMH as predictor of premature ovarian insufficiency: a longitudinal study of 120 Turner syndrome patients. Journal of Clinical Endocrinology and Metabolism 100 E1030–E1038. (https://doi.org/10.1210/jc.2015-1621)

Machado CM, De-Souza EA, De-Queiroz ALVF, Pimentel FSA, Silva GS, Gomes FM, Montero-Lomeli M & Masuda CA 2017 The galactose-induced decrease in phosphate levels leads to toxicity in yeast models of galactosemia. Biochimica et Biophysica Acta: Molecular Basis of Disease 1863 1403–1409. (https://doi.org/10.1016/j.bbadis.2017.02.032)

Machtinger R, Combesle CM, Missmer SA, Correia KE, Fox JH & Racowsky C 2012 The association between severe obesity and characteristics of failed fertilized oocytes. Human Reproduction 27 3198–3207. (https://doi.org/10.1093/humrep/des308)

Manssen LS, Kelsey TW, Ernst E, Macklon NT, Lund AM & Andersen CY 2018 Cryopreservation of ovarian tissue may be considered in young girls with galactosemia. Journal of Assisted Reproduction and Genetics 35 1209–1217. (https://doi.org/10.1007/s10815-018-2092-9)

Marino R & Misra M 2011 Bone health in primary ovarian insufficiency. Seminars in Reproductive Medicine 29 317–327. (https://doi.org/10.1055/s-0031-1280917)

Matthews SJ, Pitcon H, Ernst E & Andersen CY 2018 Successful pregnancy in a woman previously suffering from β-thalassemia following transplantation of ovarian tissue cryopreserved before puberty. Minerva Ginecologica 70 432–435. (https://doi.org/10.23736/S0002-4788.18.04240-5)

Medicine ECoATIR 2019 Fertility preservation and patient facing gonadotoxic therapies: an Ethics Committee opinion. Fertility and Sterility 110 380–386. (https://doi.org/10.1016/j.fertnstert.2018.05.034)

Meyer WR, Doyle MB, Grifo JA, Lipetz KJ, Oates PJ, Decherney AH & Diamond MP 1999 Aldose reductase inhibition prevents galactose-induced ovarian dysfunction in the Sprague-Dawley rat. American Journal of Obstetrics and Gynecology 167 1837–1843. (https://doi.org/10.1001/ajog.167.5.1837)

Mumma JO, Chhay JS, Ross KL, Eaton JS, Newell-Litwa KA & Fridovich-Keil JL 2008 Distinct roles of galactose-1P in galactose-mediated growth arrest of yeast deficient in galactose-1P uridylytransferase (GALT) and UDP-galactose 4-epimerase (GALE). Molecular Genetics and Metabolism 93 160–171. (https://doi.org/10.1016/j.mgme.2007.09.012)

Nahata L, Woodruff TK, Quinn GP, Meacham LR, Chen D, Appiah LC, Finlayson C, Orwig KE, Laronda MM, Rowell EE, et al. 2020 Ovarian tissue cryopreservation as standard of care: what does this mean for pediatric populations? Journal of Assisted Reproduction and Genetics 37 1323–1326. (https://doi.org/10.1007/s10815-020-01794-7)

Nelson LM 2009 Clinical practice. Primary ovarian insufficiency. New England Journal of Medicine 360 606–614. (https://doi.org/10.1056/NEJMc0808697)

Ning C & Segal S 2000 Plasma galactose and galactitol concentration in patients with galactose-1-phosphate uridylytransferase deficiency galactosemia: determination by gas chromatography/mass spectrometry. Metabolism: Clinical and Experimental 49 1460–1466. (https://doi.org/10.1016/S0026-0495(00)00552-2)

Nteeba J, Ross JW, Perfield JW, 2nd & Keating AF 2013 High fat diet induced obesity alters ovarian phosphatidylinositol-3 kinase signaling gene expression. Reproductive Toxicology 42 68–77. (https://doi.org/10.1016/j.reprotox.2013.07.026)

Osłowski CM & Urano F 2011 Measuring ER stress and the unfolded protein response using mammalian tissue culture system. Methods in Enzymology 490 71–92. (https://doi.org/10.1016/B978-0-12-385114-7.00004-0)

Panay N, Anderson RA, Nappi RE, Vincent AJ, Vujovic S, Webber L & Wolfman W 2020 Premature ovarian insufficiency: an International Menopause Society White Paper. Climacteric 23 426–446. (https://doi.org/10.1080/13697137.2020.1804547)
S Hagen-Lillevik, J S Rushing & al.

Primary ovarian insufficiency in galactosemia

Poiriot C, Brugieries L, Yakouben K, Prades-Borio M, Marzouk F, de Lambert G, Pacquement H, Bernaudin F, Neven B, Paye-Jaouen A, et al. 2019 Ovarian tissue cryopreservation for fertility preservation in 418 girls and adolescents up to 15 years of age facing highly gonadotoxic treatment. Twenty years of experience at a single center. Acta Obstetricia et Gynecologica Scandinavica 98 630–637. (https://doi.org/10.1111/aogs.13616)

Pystila BM, Shaw KA, Neumann SE & Fridovich-Keil JI. 2015 Newborn screening for galactosemia in the United States: looking back, looking around, and looking ahead. In JMD Reports, Vol. 15, pp. 79–93. Springer. (https://doi.org/10.1007/8904_2014_302)

Qin L, Wang Z, Tao L & Wang Y 2010 ER stress negatively regulates AKT/mTOR pathway to enhance autophagy. Autophagy 6 239–247. (https://doi.org/10.1002/auto.6.2.11062)

Reddy P, Adhihari D, Zheng W, Liang S, Hamalainen T, Tohonen V, Ogawa W, Noda T, Volarevic S, Huhtaniemi I, et al. 2009 FasK signaling in oocytes controls reproductive aging and lifespan by manipulating the survival of primordial follicles. Human Molecular Genetics 18 2813–2824. (https://doi.org/10.1093/hmg/ddp217)

Reichman ME, Judd JT, Taylor PR, Nair PP, Jones DY & Qin L, Wang Z, Tao L & Wang Y 2019 The natural history of classic galactosemia: lessons from the 177–188.

Sanchez RD, Spencer JB, Epstein MP, Pollak SV, Vardhana PA, Lustbader JW & Fridovich-Keil JI. 2009 Biomarkers of ovarian function in girls and women with classic galactosemia. Fertility and Sterility 92 344–351. (https://doi.org/10.1016/j.fertnstert.2008.04.060)

Segers I, Bardhi E, Mateiez I, Van Moer E, Schots R, Verheyen G, Tournaye H & De Vos M 2020 Live births following fertility preservation using in-vitro maturation of ovarian tissue oocytes. Human Reproduction 35 2026–2036. (https://doi.org/10.1093/humrep/dea175)

Sharif K, Wadat A, Bridgewood C, Kanduc D, Amital H & Shoenfeld Y 2019 Insights into the autoimmune aspect of premature ovarian insufficiency. Best Practice and Research: Clinical Endocrinology and Metabolism 33 101323. (https://doi.org/10.1016/j.bjem.2019.101323)

Slepak T, Tang M, Addo F & Lai K 2005 Intracellular galactose-1-phosphate accumulation leads to environmental stress response in yeast model. Molecular Genetics and Metabolism 86 360–371. (https://doi.org/10.1016/j.ymgme.2005.08.002)

Slepak TJ, Tang M, Slepak VZ & Lai K 2007 Involvement of endoplasmic reticulum stress in a novel classic galactosemia model. Molecular Genetics and Metabolism 92 78–87. (https://doi.org/10.1016/j.ymgme.2007.06.005)

Spencer JB, Badik JR, Ryan EL, Gleason TJ, Broadaway KA, Epstein MP & Fridovich-Keil JI 2013 Modifiers of ovarian function in girls and women with classic galactosemia. Journal of Clinical Endocrinology and Metabolism 98 E1257–E1265. (https://doi.org/10.1210/jc.2013-1374)

Sterling EW & Nelson LM 2011 From victim to survivor to thriver: helping women with primary ovarian insufficiency integrate recovery, self-management, and wellness. In Seminars in Reproductive Medicine, p. 353. NIH Public Access. (https://doi.org/10.1055/s-0031-1280920)

Strauss III JF & William CJ 2019 Ovarian life cycle. In Yin and Jaffe's Reproductive Endocrinology, pp. 167.e169–205.e169. Elsevier.

Sullivan SD, Sarrel PM & Nelson LM 2016 Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertility and Sterility 106 1588–1599. (https://doi.org/10.1016/j.fertnstert.2016.09.046)

Suzuki N, Yoshioka N, Takae S, Sugishita Y, Tamura M, Hashimoto S, Morimoto Y & Kawamura K 2015 Successful fertility preservation following ovarian tissue vitrification in patients with primary ovarian insufficiency. Human Reproduction 30 608–615. (https://doi.org/10.1093/humupd/dem153)

Takehara I, Igarashi H, Kawagoe J, Matsuo K, Takahashi K, Nishi M & Nagase S 2020 Impact of endoplasmic reticulum stress on oocyte aging mechanisms. Molecular Human Reproduction 26 567–575. (https://doi.org/10.1093/molehr/gaa040)

Tang M, Siddiqui A, Witt B, Yuzuyuk T, Johnson B, Fraser N, Chen W, Rascon R, Yin X, Goli H, et al. 2014 Subfertility and growth restriction in a new galactose-1-phosphate uridylyltransferase (GALT) − deficient mouse model. European Journal of Human Genetics 22 1172–1179. (https://doi.org/10.1038/ejhg.2014.12)

Thakur M, Shaeib F, Khan SN, Kohan-Ghadir HR, Jeelani R, Alsdaheri SR, Gonik B & Abu-Soud HM 2017 Galactose and its metabolites deteriorate metaphase II mouse oocyte quality and subsequent embryo development by disrupting the spindle structure. Scientific Reports 7 231. (https://doi.org/10.1038/s41598-017-00159-y)

Thakur M, Feldman G & Puscheck EE 2018 Primary ovarian insufficiency in classic galactosemia: current understanding and future research opportunities. Journal of Assisted Reproduction and Genetics 35 3–16. (https://doi.org/10.1007/s11139-017-1039-7)

Therreil Jr BL, Lloyd-Puryear MA, Camp KM & Mann MY 2014 Inborn errors of metabolism identified via newborn screening: ten-year incidence data and costs of nutritional interventions for research agenda planning. Molecular Genetics and Metabolism 113 14–26. (https://doi.org/10.1016/j.mgen.2014.07.009)
Tian T, Zhao Y, Nakajima S, Huang T, Yao J, Paton AW, Paton JC & Kitamura M 2011 Cytoprotective roles of ERK and Akt in endoplasmic reticulum stress triggered by subtilase cytotoxin. Biochemical and Biophysical Research Communications 410:852–858. (https://doi.org/10.1016/j.bbrc.2011.06.078)

van Erven B, Gubbels CS, van Golde RJ, Dunselman GA, Derhaag JG, de Wert G, Geraedts JP, Bosch AM, Treacy EP, Welt CK, et al. 2013 Fertility preservation in female classic galactosemia patients. Orphanet Journal of Rare Diseases 8:107. (https://doi.org/10.1186/1750-1172-8-107)

van Erven B, Berry GT, Cassiman D, Connolly G, Forca M, Gautschi M, Gubbels CS, Hollak CEM, Janssen MC, Knerr I, et al. 2017 Fertility in adult women with classical galactosemia and primary ovarian insufficiency. Fertility and Sterility 108:168–174. (https://doi.org/10.1016/j.fertnstert.2017.05.013)

van Kasteren YM & Schoemaker J 1999 Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Human Reproduction Update 5:483–492. (https://doi.org/10.1093/humupd/5.5.483)

Vanoevelen JM, van Erven B, Bierau J, Huang X, Berry GT, Vos R, Coelho AI & Rubio-Gozalbo ME 2018 Impaired fertility and motor function in a zebrafish model for classic galactosemia. Journal of Inherited Metabolic Disease 41:117–127. (https://doi.org/10.1007/s10545-017-0071-1)

Vinogrova VA, Coupland C & Hipsiplex-Cox J 2019 Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ 364:k4810. (https://doi.org/10.1136/bmj.k4810)

Wada Y, Kikuchi A, Arai-Ichinomi N, Sakamoto O, Takezawa Y, Iwasawa S, Niihori T, Niyazuki H, Nakajima Y, Ogawa E, et al. 2019 Biallelic GALM pathogenic variants cause a novel type of galactosemia. Genetics in Medicine 21:1286–1294. (https://doi.org/10.1038/s41368-018-0340-x)

Waisbren SE, Potter NL, Gordon CM, Green RC, Greenstein P, Gubbels CS, Rubio-Gozalbo E, Schomer D, Welt C, Anastasoaie A, et al. 2012 The adult galactosemic phenotype. Journal of Inherited Metabolic Disease 35:279–286. (https://doi.org/10.1007/s10545-011-9372-y)

Wang N, Luo LL, Xu JJ, Xu MY, Zhang XM, Zhou XL, Liu WJ & Fu YC 2014 Obesity accelerates ovarian follicle development and follicle loss in rats. Metabolism: Clinical and Experimental 63:94–103. (https://doi.org/10.1016/j.metabol.2013.09.001)

Webb AL, Singh RH, Kennedy MJ & Elsaj J 2003 Verbal dyspraxia and galactosemia. Pediatric Research 53:396–402. (https://doi.org/10.1203/01.PDR.0000094966.19532.1B)

Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, de Muinck Keizer-Schrama S & Hogervorst E 2016 ESHRE Guideline: management of women with premature ovarian insufficiency. Human Reproduction 31:926–937. (https://doi.org/10.1093/humrep/dew027)

Webber L, Anderson RA, Davies M, Jansse F & Vermeulen N 2017 HRT for women with premature ovarian insufficiency: a comprehensive review. Human Reproduction Open 2017: hox007. (https://doi.org/10.1093/hropen/hox007)

Welling L, Bernstein LE, Berry GT, Burlina AB, Eyskens F, Gautschi M, Grünewald S, Gubbels CS, Knerr I, Labrune P, et al. 2017 International Clinical Guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. Journal of Inherited Metabolic Disease 40:171–176. (https://doi.org/10.1007/s10545-016-9990-5)

Wright CJ, Cari EL, Sandoval J, Bales E, Sam PK, Zarate MA, Polotsky AJ, Kallen AN & Johnson J 2020 Control of murine primordial follicle growth activation by Ihe/NfI8 signaling. Reproductive Sciences 27:2063–2074. (https://doi.org/10.1177/1933719119852000-00225-3)

Wu LL, Dunning KR, Yang X, Russell DL, Lane M, Norman RJ & Robker RL 2010 High-fat diet causes lipotoxicity responses in cumulus-oocyte complexes and decreased fertilization rates. Endocrinology 151:5438–5445. (https://doi.org/10.1210/en.2010-0551)

Wu LL, Russell DL, Norman RJ & Robker RL 2012 Endoplasmic reticulum (ER) stress in cumulus-oocyte complexes impairs pentraxin-3 secretion, mitochondrial membrane potential (DeltaPsi m), and embryo development. Molecular Endocrinology 26:562–573. (https://doi.org/10.1210/me.2011-1362)

Wu LL, Russell DL, Wong SI, Chen M, Tsai TS, St John JC, Norman RJ, Febbraio MA, Carroll J & Robker RL 2015 Mitochondrial dysfunction in oocytes of obese mothers: transmission to offspring and reversal by pharmacological endoplasmic reticulum stress inhibitors. Development 142:681–691. (https://doi.org/10.1242/dev.14850)

Xiong Y, Chen H, Lin P, Wang A, Wang J & Jin Y 2017 AT1F6 knockdown decreases apoptosis, arrests the S phase of the cell cycle, and increases steroid hormone production in mouse granulosa cells. American Journal of Physiology: Cell Physiology 312:C341–C353. (https://doi.org/10.1152/ajpcell.00222.2016)

Yan H, Zhang J, Wen J, Wang Y, Niu W, Teng Z, Zhao T, Dai Y, Zhang Y, Wang C, et al. 2018 CDC42 controls the activation of primordial follicles by regulating PI3K signaling in mouse oocytes. BMC Biology 16:73. (https://doi.org/10.1186/s12915-018-0541-4)

Yoon SH, Choi YM, Hong MA, Kim JJ, Lee GH, Hwang KR & Moon SY 2013 Association study of anti-Mullerian hormone and anti-Mullerian hormone type II receptor polymorphisms with idiopathic primary ovarian insufficiency. Human Reproduction 28:3301–3305. (https://doi.org/10.1093/humrep/det384)

Yuzuyuk T, Vaila K, Andrews A, Pasquali M & Longo N 2018 Biochemical changes and clinical outcomes in 34 patients with classical galactosemia. Journal of Inherited Metabolic Disease 41:197–208. (https://doi.org/10.1007/s10545-018-0316-9)

Zhai M, Feng F, Chu C, Vue W & Li L 2019 A novel EIF4ENIF1 mutation associated with a diminished ovarian reserve and premature ovarian insufficiency identified by whole-exome sequencing. Journal of Ovarian Research 12:119. (https://doi.org/10.1186/s13048-019-0595-0)

Zhou S, Yan W, Shen W, Cheng J, Xi Y, Yuan S, Fu F, Ding T, Luo A & Wang S 2018 Low expression of SEMA6C accelerates the primordial follicle activation in the neonatal mouse ovary. Journal of Cellular and Molecular Medicine 22:486–496. (https://doi.org/10.1111/jcmm.13337)

Received in final form 9 June 2021
Accepted 25 June 2021
Accepted Manuscript published online 25 June 2021