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REVIEW

Primary ovarian insufficiency in classic galactosemia: current understanding and future research opportunities

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Abstract Classic galactosemia is an inborn error of the metabolism with devastating consequences. Newborn screening has been successful in markedly reducing the acute neonatal symptoms from this disorder. The dramatic response to dietary treatment is one of the major success stories of newborn screening. However, as children with galactosemia achieve adulthood, they face long-term complications. A majority of women with classic galactosemia develop primary ovarian insufficiency and resulting morbidity. The underlying pathophysiology of this complication is not clear. This review focuses on the reproductive issues seen in girls and women with classic galactosemia. Literature on the effects of classic galactosemia on the female reproductive system was reviewed by an extensive Pubmed search (publications from January 1975 to January 2017) using the keywords: galactosemia, ovarian function/dysfunction, primary ovarian insufficiency/failure, FSH, oxidative stress, fertility preservation. In addition, articles cited in the search articles and literature known to the authors was also included in the review. Our understanding of the role of galactose metabolism in the ovary is limited and the pathogenic mechanisms involved in causing primary ovarian insufficiency are unclear. The relative rarity of galactosemia makes it difficult to accumulate data to determine factors defining timing of ovarian dysfunction or treatment/fertility preservation options for this group of women. In this review, we present reproductive challenges faced by women with classic galactosemia, highlight the gaps in our understanding of mechanisms leading to primary ovarian insufficiency in this population, discuss new advances in fertility preservation options, and recommend collaboration between reproductive medicine and metabolic specialists to improve fertility in these women.

Keywords Classic galactosemia · Primary ovarian insufficiency · Ovarian dysfunction · Galactose metabolism · Fertility preservation

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Introduction

Case presentation

A 22-year-old woman with classic galactosemia presents a history of secondary amenorrhea for 5 years. Galactosemia was diagnosed by newborn screening. Confirmatory testing showed that she had absent galactose-1-P uridylyltransferase (GALT) enzyme activity and was homozygous for the Q188R pathogenic variant (missense variant c.563A > G {p.Gln188Arg}) in the *GALT* gene. Strict dietary modification (mainly elimination of galactose from her diet) was instituted on day 4 of life. She is compliant with galactose-restricted diet and reports no other medical conditions. She has some speech problems and a mild tremor. Her puberty was normal in onset

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and development. Her menarche was at 12 years of age and she had regular periods. Her periods became irregular at 15 years of age and she developed amenorrhea at age 16. Her follicle-stimulating hormone (FSH) level was noted to be > 100 IU/L on two separate occasions, 1 month apart, which is consistent with the menopausal range. Questions to consider regarding her reproductive health:

- How should she be evaluated and treated?
- What is her prognosis for a spontaneous pregnancy?
- What are her options for fertility preservation?

Primary ovarian insufficiency

Primary ovarian insufficiency (POI), previously referred to as premature ovarian failure (POF) or premature menopause (terms that are no longer recommended), is a condition used to describe a continuum of impaired ovarian function, eventually leading to a premature cessation of menstruation in young women [1]. It is characterized by the occurrence of amenorrhea for 3 months or more before the age of 40, elevated FSH to menopausal levels (> 40 IU/L) on at least two tests obtained 1 month apart, and low estradiol levels < 50 pg/ml [2]. Estimates that POI affects 1% of the female population are based on a study from Rochester, Minnesota, in 1986 [3]. This study estimated that POI affects 1 in 10,000 by age 20, 1 in 1000 by age 30, and 1 in 100 women by age 40. POI is characterized by deficiency of estrogen and elevation of FSH. It presents with irregular menstrual cycles, oligomenorrhea or amenorrhea and leads to infertility as well as complications related to hypoestrogenism (menopausal symptoms, decreased bone mineral density, and increased risk of cardiovascular morbidity) and emotional distress [4]. It is a life-altering diagnosis. In 90% of cases, the cause remains unknown [2]. In cases where a diagnosis is made, causes include genetic causes (Table 1) (X chromosome abnormalities, Turner's syndrome, fragile X premutation, mutations in specific genes [5–29], autoimmune causes (Addison's disease, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, dry eye syndrome and autoimmune polyglandular syndrome), chemotherapy, radiotherapy, viral oophritis (mumps, HIV seropositivity), metabolic causes (Table 2) (classic galactosemia, PMM2-congenital disorder of glycosylation, 17-hydroxylase deficiency) and toxin exposure [30, 31]. In addition, POI is a phenotypic presentation of mendelian disorders and genetic syndromes: Blepharophimosis, ptosis, epicanthus inversus type I syndrome (autosomal dominant, caused by pathogenic variants in *FOXL2*), autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (autosomal recessive (AR), caused by pathogenic variants in *AIRE* gene), Perrault syndrome (AR, caused by pathogenic variants in one of several genes: *TWNK*, *CLPP*, *HARS2*, *LARS2*, or *HSD17B4*), and ovarioleukodystrophies (AR, pathogenic variants in *EIF2B2*, *EIF2B4* or *EIF2B5*).

Galactosemia and POI

A majority of women with classic galactosemia develop POI over the course of their life despite a galactose-restricted diet [32–34]. Although galactosemia is a rare disorder and the number of affected individuals is small, diagnosis and management of POI in women with galactosemia present challenges that highlight gaps in our understanding. A better understanding of the pathophysiology of POI in galactosemia will not only improve the management of women with this disorder, it will increase our understanding of intricacies of ovarian function in general.

Methods

This review focuses on the reproductive issues seen in girls and women with classic galactosemia. Literature on the effects of classic galactosemia on the female reproductive system was reviewed by an extensive Pubmed search (publications from January 1975 to January 2017) using the keywords galactosemia, ovarian function/dysfunction, primary ovarian insufficiency/failure, FSH, oxidative stress, and fertility preservation. In addition, articles cited in the search articles and literature known to the authors was also included in the review.

Results and discussion

Pathophysiology of galactosemia

Galactosemia is a rare inborn error of metabolism caused by the deficiency of enzymes involved in galactose metabolism [35]. Galactose is a hexose monosaccharide mainly derived from lactose, a disaccharide sugar found mainly in milk and dairy products. Galactose is also produced endogenously in the human body [36]. In addition to providing calories, galactose and its derivatives are required for glycoconjugates (carbohydrates covalently linked to amino acids, proteins, lipids and other small molecules) that are key elements of cell membrane structure, hormones, extracellular matrix, immunologic determinants and structural elements of central nervous system [37, 38]. Galactose is catabolized by the Leloir pathway (Fig. 1) and requires three key enzymes galactokinase (GALK), galactose-1-P uridylyltransferase (GALT), and UDP-galactose 4-epimerase (GALE). Classic galactosemia, the most common and severe form of this condition, is caused by the deficiency of GALT (OMIM 606999). This autosomal recessive disorder affects about 1 in 40,000 to 60,000 newborns. The *GALT* gene is located on chromosome 9p13 and

Table 1 Genetic abnormalities associated with POI

1. Chromosomal abnormalities

Monosomy X (Turner syndrome)

Trisomy X

X chromosome mosaicism

Balanced X/autosomal translocation

X chromosome deletions including deletion of Xp13 region

2. Potential genes on X chromosome

Gene	Location	Function of protein encoded by gene[a]	Selected references
FMR1	Xq27.3	Binds RNA and is associated with polysomes. May be involved in mRNA trafficking from the nucleus to the cytoplasm.	[5, 6]
BMP15	Xp11.2	Oocyte-specific growth/differentiation factor that stimulates folliculogenesis and granulosa cell growth.	[7]
PGRMC1	Xq24	Membrane-associated progesterone steroid receptor.	[8]
AR	Xq12	Androgen receptor.	[9]
FOXO4	Xq13.1	Transcription factor involved in the regulation of the insulin-signaling pathway.	[10]
POF1B	Xq21.1	Organization of epithelial monolayers by regulating the actin cytoskeleton. May be involved in development of the ovary.	[11]
DACH2	Xq21.2	Transcription factor involved in regulation of organogenesis.	[12]
DIAPH2	Xq21.33	Role in the development and normal function of the ovaries.	[13]

3. Potential genes on autosomes

Gene	Location	Function of protein encoded by gene[a]	Selected references
FSHB	11p14.1	Beta subunit of follicle-stimulating hormone. Stimulates development of follicles.	[14]
FSHR	2q16.3	Receptor for follicle-stimulating hormone	[15]
LHB	19q13.33	Beta subunit of luteinizing hormone	[16]
LHCGR	2p16.3	Luteinizing hormone/choriogonadotropin receptor	[16]
INHA	2q25	Alpha subunit of the inhibin A and B protein complexes	[17]
GDF-9	5q31.1	Required for ovarian folliculogenesis. Promotes primordial follicle development.	[7]
FIGLA	2p13.3	Germline specific transcription factor implicated in postnatal oocyte-specific gene expression.	[18]
NOBOX	7q35	Transcription factor that may play a role in oogenesis.	[19]
NR5A1	9q33.3	Transcriptional activator involved in sex determination.	[20]
STAG3	7q22.1	Subunit of the cohesin complex which regulates the cohesion of sister chromatids during cell division	[21]
HFM1	1p22.2	ATP-dependent DNA helicase. Expressed mainly in germline cells. Required for crossover formation and complete synapsis of homologous chromosomes during meiosis.	[22]
MCM8	20p12.3	Involved in homologous recombination repair following DNA interstrand cross-links. Key role during gametogenesis.	[23]
MCM9	6q22.31	Involved in homologous recombination repair following DNA interstrand cross-links. Key role during gametogenesis.	[24]
MSH5	6q21.33	Involved in DNA mismatch repair and meiotic recombination.	[25]
ERCC6	10q11.23	Involved in transcription-coupled nucleotide excision repair	[26]
SYCE1	10q26.3	Member of the synaptonemal complex, which links homologous chromosomes during prophase I of meiosis.	[27]

FMR1 fragile X mental retardation 1; *BMP15* bone morphogenetic protein 15; *PGRMC1* progesterone receptor membrane component-1; *AR* androgen receptor; *FOXO4* forkhead box O4; *POF1B* premature ovarian failure, 1B; *DACH2* dachshund family transcription factor 2; *DIAPH2* diaphanous homolog 2 (Drosophila); *FSHB* follicle-stimulating hormone beta subunit; *FSHR* follicle-stimulating hormone receptor; *LHB* luteinizing hormone beta polypeptide; *LHCGR* luteinizing hormone/choriogonadotropin receptor; *INHA* inhibin alpha subunit; *GDF-9* growth differentiation factor 9; *FIGLA* folliculogenesis-specific BHLH transcription factor; *NOBOX* newborn ovary homeobox-encoding; *NR5A1* nuclear receptor subfamily 5 group A member 1; *STAG3* stromal antigen 3; *HFM1* ATP-dependent DNA helicase homolog; *MCM8* minichromosome maintenance 8 homologous recombination repair factor; *MCM9* minichromosome maintenance 9 homologous recombination repair factor; *MSH5* MutS homolog 5; *ERCC6* excision repair cross-complementation group 6; *SYCE1* synaptonemal complex central element protein 1

[a] Genecards URL: http://www.genecards.org/

over 230 variants have been identified [39]. The most prevalent pathogenic variant in the Caucasian population is Q188R (missense variant c.563A > G {p.Gln188Arg}) and for African Americans, S135L is the most frequent pathogenic

Table 2 Metabolic disorders associated with POI

Disorder	OMIM number	Gene	Location	Features
Galactosemia	230,400	*GALT*	9p13.3	Failure to thrive Vomiting, diarrhea Hepatomegaly Susceptibility to *E. coli* sepsis Cognitive impairment Primary ovarian insufficiency
Congenital disorders of glycosylation type 1A	212,065	*PMM2*	16p13.2	Failure to thrive Microcephaly (50% of patients) Prominent forehead, large ears Eye abnormalities: strabismus, retinitis pigmentosa Neurological abnormalities: Seizures, ataxia, hyperreflexia, hypotonia Joint contractures
Congenital adrenal hyperplasia due to 17α-hydroxylase deficiency	202,110	*CYP17A1*	10q24.32	Ambiguous genitalia Primary amenorrhea Male pseudohermaphroditism Hypertension Hypokalemic alkalosis
Aromatase deficiency	613,546	*CYP19A1*	15q21.2	Maternal virilization in pregnancy Pseudohermaphroditism in female infants Cystic ovaries, delayed bone maturation Primary amenorrhea Hypergonadotropic hypogonadism.

GALT galactose-1-phosphate uridyl transferase; *PMM2* phospomannomutase 2; *CYP17A1* cytochrome P450, family 17, subfamily A, polypeptide 1; *CYP19A1* cytochrome P450, family 19, subfamily A, polypeptide 1; *OMIM* online Mendelian inheritance in man

variant. Many allelic variants are associated with partial enzyme defects. Best known is the D2 Duarte variant (N134D2), *GALT* gene polymorphism that exists in *cis*, with a small deletion in the 5′ flanking region [39]. Duarte galactosemia is a mild variant of GALT deficiency where affected individuals carry one severe, or G allele of the *GALT* gene and one Duarte, or D/D2, allele. This variant results in 25% normal GALT enzyme activity levels as compared to classic galactosemics, who demonstrate < 1% of normal GALT activity levels [35].

In classic galactosemia, severe deficiency of GALT leads to accumulation of galactose and its metabolites, which have toxic effects in the body. Newborns with this disorder develop vomiting, diarrhea, jaundice, failure to thrive, rapidly escalating into liver and renal disease, cataracts, and life-threatening sepsis if they continue to ingest breast milk or cow's milk formula, which contain large amounts of lactose. Treatment involves substituting soymilk formula (soy products are galactose free) in place of breast milk or cow's milk. Treatment has to begin as soon as possible to avoid these complications; consequently, galactosemia testing at birth is part of newborn screening programs in all states in the United States of America [40]. As a result, infants with galactosemia are detected within days of being born and immediate lifelong restriction of galactose in the diet is implemented. This intervention has significantly reduced the incidence of acute life-threatening disease in the newborn, yet long-term complications still occur in patients with classic galactosemia despite dietary restrictions. These complications include mild growth retardation, intellectual deficits, speech delay, decreased bone density, movement disorders and ovarian dysfunction in females [34]. Galactosemia does not impact testicular function in males.

Ovarian dysfunction in classic galactosemia

The association of galactosemia with POI was first reported in 1979 when three letters noting the complication were published [41–43]. In 1981, Kaufman et al. studied 18 female and eight male patients with galactosemia [44]. The gonadal function was normal in the males, but 67% females (12/18) had signs of hypergonadotropic hypogonadism. Laboratory testing obtained after onset of oligomenorrhea or amenorrhea showed that serum FSH levels were elevated in most with a range of 12.3 to 167 IU/L (FSH level > 10 IU/L indicate diminished ovarian reserve and FSH > 40 IU/L are seen in patients with premature ovarian failure). Serum LH levels ranged between 12.7 and 114 IU/L. Serum estradiol levels were decreased, ranging from < 5 to 116.0 pg/mL. Ultrasonography of the pelvis demonstrated small or absent ovaries. The same investigators followed 26 women with

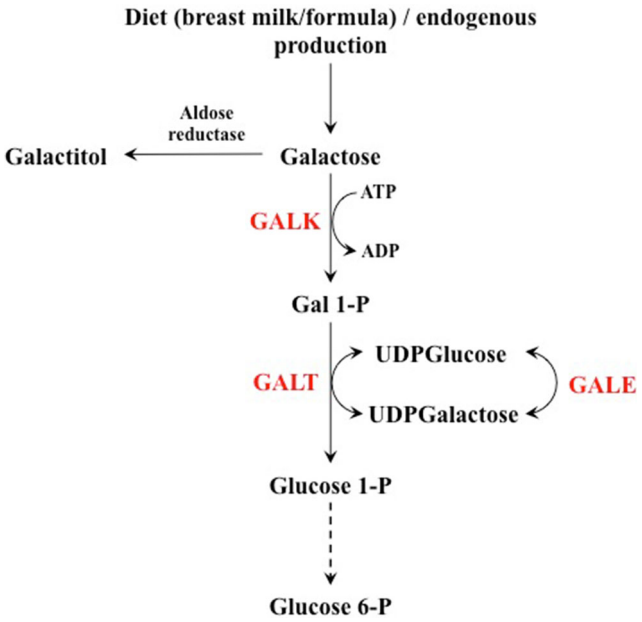

Fig. 1 Pathway of galactose metabolism (simplified). GALE, UDP galactose 4′-epimerase; GALK, galactokinase; GALT, galactose-1-P uridyltransferase; P, phosphate; UDP, uridine diphosphate; broken lines show pathway with multiple enzymatic steps

classic galactosemia over a 4 year period [45]. Twelve female patients with ovarian failure documented at the beginning of this study continued to have either primary or secondary amenorrhea on follow-up. Five of six patients, who previously had a normal gonadal function, developed either hypergonadotrophic hypogonadism or an abnormal response to gonadotrophin-releasing hormone indicative of acquired ovarian damage. Seven of eight female patients, 1–12 years of age, who were evaluated for the first time, had an exaggerated release of gonadotrophins during gonadotrophin-releasing hormone stimulation tests diagnostic of gonadal insufficiency. Hence, 90% of the patients showed signs of hypergonadotropic hypogonadism over the 4-year study period. Since then, POI in women with classic galactosemia has been extensively studied.

In women with classic galactosemia, hypergonadotropic hypogonadism is usually diagnosed in the second decade of life or even earlier. Serum FSH levels are often elevated early in life (4 months to 4 years) and between early childhood to the onset of puberty (5–12 years). Hypoestrogenism is usually present. Serum LH levels can be normal or increased.

Ultrasound appearance of the ovaries in various studies include the full range: normal sized ovaries [44, 46], small ovaries [44, 45, 47–49], streak ovaries [50–52], and absent ovaries [44, 47, 50, 53]. In one study, ovarian volume was evaluated by MRI in 14 patients and compared to age matched controls, prepubertal controls and postmenopausal controls [54]. The ovarian volumes of girls with galactosemia were smaller than those of age matched controls (p = 0.001) and prepubertal girls (0.008). These volumes did not differ significantly from postmenopausal controls (p = 0.161).

In patients where laparoscopy was performed, visualization of the ovaries showed hypoplastic/streak ovaries [41, 44, 46, 52, 55, 56]. There are case reports of normal sized ovaries as in a 26-year-old patient with oligomenorrhea and secondary amenorrhea. Interestingly, the sentinel study by Kaufman et al. [44] described one galactosemic patient with normal ovaries visualized at 7 years of age, but streak ovaries by age 17 noted on laparoscopy.

Histological analysis of the ovaries has been reported in case reports [34, 46, 49, 51, 52, 55–58] and reviewed in one study [34]. Two female newborns have been reported with morphologically normal ovaries with normal folliculogenesis [57, 58]. In a 17-year-old patient with hypergonadotropic hypogonadism, ovaries were noted to be reduced to two strips of fibrous stroma almost devoid of follicles [51]. In another 17-year-old patient with primary amenorrhea, histological examination of one complete ovary showed ovarian stroma and a small group of hilar cells. No follicles were present [55]. Biopsy of the ovary in a 21-year-old female with classic galactosemia noted smooth muscle and fibrous tissue with an absence of ovarian parenchyma [52]. Other studies have noted rare and atretic primordial follicles with absence of Graafian follicles [46, 49, 59].

Galactose metabolism in the ovary

The male reproductive system is relatively unaffected by adverse effects of classic galactosemia [34]. In comparison, ovarian function in female patients is exquisitely sensitive to these effects. The reason for this differential damage remains unclear. There is a tissue-specific variation in the GALT mRNA levels and enzyme activity [60]. The liver has the highest GALT mRNA and activity, followed by the kidney, ovary, and heart; skeletal muscle and testis have the least GALT mRNA levels and enzyme activity [60]. In fact, the ovary is one of the organs where enzymes involved in galactose metabolism (GALK, GALT, GALE and UDP-glucose phosphorylase) are relatively abundant [60, 61]. It is not clear, whether this relative abundance of galactose-metabolizing enzymes indicates a differential requirement of the ovary for disposition of galactose or whether GALT or galactose metabolism, in general, has a yet unknown function in the ovary [32]. In human studies, active metabolism of galactose has been noted in the ovarian tissue [61] and the concentration of galactose in the preovulatory follicular fluid correlated with plasma levels [62]. However, our knowledge of galactose uptake and metabolism by different cells in the ovary is lacking. Future studies investigating the role of galactose metabolism in various ovarian cells including oocytes utilizing omics techniques (transcriptomics, proteomics and metabolomics {both steady state and metabolic flux analysis}) might help close the

knowledge gap and illuminate how complex perturbations in galactose metabolites affect ovarian function.

Pathophysiology of POI in galactosemia

Several mechanisms have been postulated to explain POI in patients with galactosemia, including toxic effects of galactose and its metabolites on the ovary, aberrant function of FSH and FSH receptor due to glycosylation abnormalities, deficiency of GALT leading to ovarian dysfunction and epigenetic mechanisms [32, 34, 63] (Fig. 2). However, an exact pathophysiology for this complication has not been elucidated. The timing of the ovarian damage is also unknown. Ovarian dysfunction has been seen in newborns, infants, and young children, raising the suspicion that these insults may have been initiated prenatally or early in development [34].

Proposed mechanisms of POI in galactosemia [reviewed in [32]] include (1) apoptosis of oocytes and/or ovarian stromal cells by galactose 1-phosphate, galactitol or galactose 1-phospate and galactitol together or from a yet unknown galactose metabolite, (2) UDP galactose deficiency in oocytes and/or ovarian stromal cells results in cell death and progressive destruction, (3) ovarian damage is secondary to abnormal FSH molecule due to defective glycosylation, (4) GALT may perform another role in the ovary other than catalyzing the conversion of galactose and deficiency of GALT in galactosemia may induce ovarian damage and (5) epigenetic mechanisms [34].

A. Toxic damage to ovaries by galactose and its metabolites

Galactose and its metabolites, most importantly galactose 1-phosphate and galactitol, have been implicated in toxic damage to the ovaries. Chronic galactose administration to rats delayed the onset of puberty, decreased normal ovulatory response, and sustained high level of FSH and low estrogen. Surprisingly, there was a striking reduction in oocyte number in the offspring of these animals, suggesting a transgenerational effect [64]. Subfertility was noted in the *GALT* gene trapped/deficient mouse model [65]. D-galactose administration in animal models induces changes resembling aging and have been linked to mitochondrial dysfunction and oxidative stress [66–68]. Indeed, galactose metabolites like galactitol are poorly metabolized in galactosemia and accumulation in ovarian cells causes swelling and cell dysfunction [69]. Galactose may also cause accumulation of reactive oxidants, like methylglyoxal that hamper the glutathione redox cycle causing damage to the ovarian cells [70]. Recent studies have demonstrated the generation of oxidative stress by exposure to galactose and its metabolites resulting in follicular dysfunction [65, 71]. Gene dysregulation, both systemically and in ovarian tissue, due to toxic levels of galactose has also been reported in galactosemia [72, 73]. However, the exact mechanism of ovarian damage in this disorder remains unclear. Therefore, very little is known why, despite the neonatal diagnosis and strict lifelong restriction of galactose, a majority of girls and women with this disorder suffer from POI.

B. FSH dysfunction

FSH inactivity due to secondary hypoglycosylation has been suggested as a potential mechanism [54, 63].

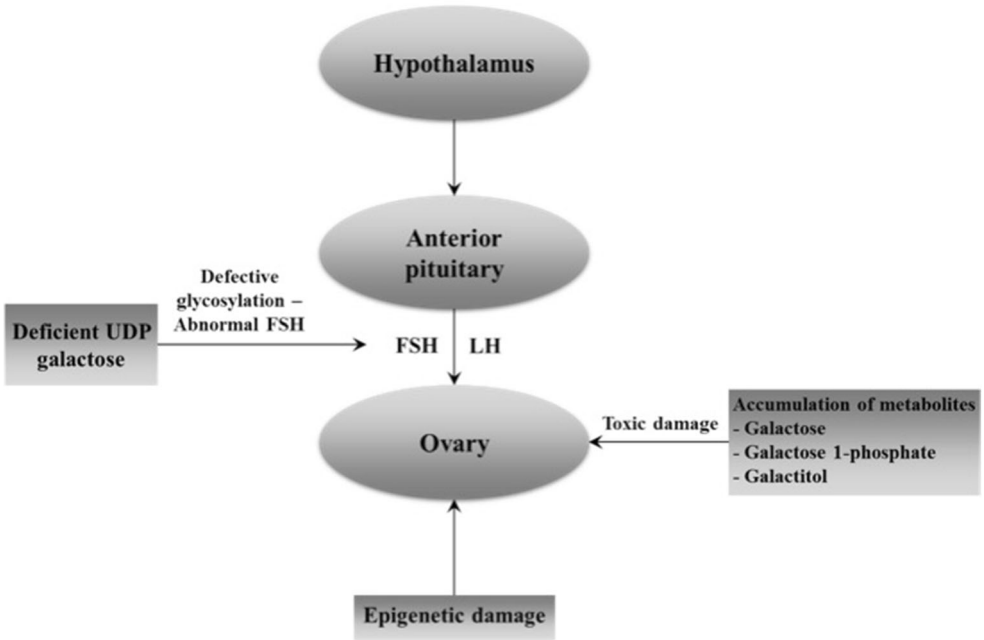

Fig. 2 Proposed mechanisms of primary ovarian insufficiency (POI) in classic galactosemia: A scheme of development of POI in women with classic galactosemia based on the current evidence is proposed. Galactose and its metabolites have been implicated in toxic damage to the ovaries. The timing of this damage remains unclear. In addition, abnormalities in follicle-stimulating hormone or its receptor and disturbances in epigenetic mechanisms have also been suggested to cause POI

FSH is a dimeric glycoprotein hormone with a protein core and complex carbohydrate chains. The majority of the asparagine-linked oligosaccharides in the human FSH are mono-, di-, and tri-sialylated biantennary structure that confirms an overall negative charge [74]. FSH undergoes extensive post-translational modification, such as glycosylation. Glycans attached to the α-subunit are critical for dimer assembly, integrity, and secretion, as well as for signal transduction. The β-subunit glycans are also important for dimer assembly and secretion, but they play a crucial role in the clearance of the dimer from the circulation [74]. UDP-galactose is required in glycosylation of gonadotropins including FSH. In classic galactosemia, intracellular concentrations of galactose 1-phospahate inhibit UDP-hexose pyrophosphorylases and reduce the intracellular concentrations of UDP-hexoses leading to a low UDP-galactose/UDP-glucose ratio [75]. Also, galactose 1-phosphate inhibits galactosyltransferase and disturbs glycosylation [76]. However, Gubbels et al. did not find a significantly altered (less acidic) distribution of FSH isoforms in galactosemic patients [77]. In another study, 15 patients underwent ovarian stimulation with exogenous gonadotropins and results showed that all but one patient had a low or no estradiol response. The authors suggest that FSH inactivity may not play a causative role in POI in this disorder [54], however, no response to exogenous gonadotropins may also imply ovarian exhaustion.

C. Epigenetic mechanisms

Disturbance of expression of genes involved in follicular development has been proposed as a possible mechanism [34, 63]. Lai et al. proposed the human tumor suppressor gene coding for GTP-binding protein Di-Ras3 (*DIRAS3*), also known as aplysia ras homology member I (*ARHI*) as a new target of galactose toxicity in patients with classic galactosemia [78]. It was one of the three genes (among 36,000+ transcripts queried) that were consistently upregulated in galactose-challenged, GALT-knockout cells, at both low and high concentrations of galactose challenge and over time [78]. Another factor associated with a possible role in galactose-related ovarian toxicity is growth differentiation factor-9 (GDF-9), an obligatory growth factor during folliculogenesis [34]. In a study by Liu et al. [79], immature Long-Evans rats (n = 10) were fed a diet consisting of 20% galactose for 19 days and GDF-9 expression was investigated by immunohistochemistry and immunoblot assay. Galactose treatment did not affect the onset of puberty as marked by the time of vaginal opening in these rats. The galactose diet significantly decreased the number of healthy growing follicles. The results of immunoblot assay showed that both bands corresponding to pro-peptide and mature forms of GDF-9 decreased with the galactose diet, about 90 and 70%, respectively. The results of immunohistochemical staining showed that the GDF-9 positive follicle number and the ratio of GDF-9 positive to GDF negative (primordial/non-growing) follicles significantly decreased with this high galactose diet. This study suggested that a high galactose diet inhibits follicular development, possibly through down-regulation of GDF-9 in the rat ovary, implying that GDF-9 may be involved in galactose-related ovarian toxicity. At this point, evidence is lacking to clearly delineate whether the down-regulation of GDF9 is the cause or the result of abnormal follicular development.

Clinical presentation and course

The clinical manifestations may include primary or secondary amenorrhea, oligomenorrhea, delayed or absence of pubertal development, subfertility and infertility [33]. Most patients and their parents are told that they will struggle with POI and will most likely have infertility. This devastating complication represents a great psychological burden for both the patients and their families [80]. However, the course of POI in females affected with galactosemia is fluctuating. A case that highlights the fluctuating nature of the ovarian function describes a woman with classic galactosemia, who had three spontaneous pregnancies [48]. She had spontaneous menarche followed by irregular cycles. At age 19, her FSH level was 42 IU/L and E2 was 0.01 pg/mL. She conceived spontaneously at 21 years of age but had an intrauterine fetal demise. She had amenorrhea following the pregnancy and evidence of POI on laboratory testing (FSH of 84 IU/L, LH 46 IU/L and E2 level of < 0.04 pg/mL). Despite these findings, she conceived spontaneously again at age 22 and delivered a healthy son. At age 25, she had undetectable levels of AMH (< 0.1 microgram/L) and no estrogen response to exogenous FSH ovarian reserve test. Despite signs of poor ovarian reserve, she again conceived and delivered a healthy child. Similarly, in a recent study where 85 women with classic galactosemia and POI were studied, 42.9% (9/21 women trying to get pregnant) conceived spontaneously. This pregnancy rate was significantly higher than that reported for women with POI from other causes (5–10%) [81]. Hence, the counseling of the patient with classic galactosemia and her family about the chances of pregnancy is complicated. Interestingly, limited evidence suggests that girls and women with Duarte variant galactosemia are not at increased risk for POI [82].

Galactosemia and pregnancy

There are over 50 or so case reports of pregnancies in women with galactosemia [83]. Data regarding the safety of pregnancy and breastfeeding in women with classic galactosemia and

their offspring is sparse. Biochemical monitoring of pregnancy and breastfeeding in five patients with classic galactosemia showed subtle and insignificant increases of galactose metabolite concentrations during pregnancy [84]. After delivery, a moderate increase of metabolite concentrations was noted. The authors concluded that specific metabolic monitoring is apparently not required in pregnant galactosemic women, and breastfeeding of the nongalactosemic offspring can be recommended. However, the long-term effects of this increase of galactose metabolites on the health of the mother (neurocognitive function, bone mineral density and ovarian function) have not been studied.

Although long-term follow-up data is not available, most infants born to galactosemic mothers reported in the literature have been healthy. An increase in the level of galactitol in maternal serum, resulting in an increase in levels in amniotic fluids, has been reported [85, 86]. In a patient who remained lactose- and galactose-free in pregnancy, the concentration of galactitol in amniotic fluid at birth was 64.0 micromol/L (reference 0.44–1.2) [85]. Cord blood galactitol was 15.0 micromol/L (reference 0.17–0.91). The infant was heterozygous for galactosemia and developed normally. In another patient, amniotic fluid galactitol was 23.5 micromol/L (control 0.44–1.2) [86]. Intrauterine fetal demise was noted at 36 weeks in a patient with classic galactosemia who had a total of 3 spontaneous pregnancies [48]. Autopsy revealed a child with a normal birth weight (25th–50th percentile), normal features, and early signs of hypoxia. An intervillositis and terminal villus deficiency were discovered, but no specific cause for this placenta abnormality could be identified. A relationship between galactosemia and fetal death was neither found nor completely excluded. In a subsequent pregnancy, estradiol and progesterone levels were followed. The levels were normal in the second trimester but decreased in the third trimester and showed a premature drop on the day before delivery. The authors concluded that this drop might explain the intrauterine death of her first child. They suggested that it might be important to check E_2 levels in the last trimester in pregnant women with classic galactosemia.

Management of POI in women with classic galactosemia

Because of the paucity of information, guidelines for screening and management of POI in a girls and women with classic galactosemia are based on expert opinion (International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up, Recommendations #28) [87]. These guidelines recommend annual monitoring for menstrual abnormalities, secondary amenorrhea, and symptoms of POI in girls and women who have gone through puberty and established regular menstrual periods. A serum FSH is recommended if there is any change in menses or POI symptoms. The guidelines do not recommend imaging by pelvic ultrasound or MRI. Although an AMH level may not predict which women are at risk for developing POI, it may be helpful in identifying women at risk for imminent POI when it is undetectable.

Based on a survey of 13 healthcare providers who follow patients with classic galactosemia from 11 countries, 10 providers had reported experiences managing teenage patients [88]. All nine providers who had female adolescent patients followed ovarian function. The main biomarkers followed for assessment of ovarian function are FSH, LH and/or estradiol. None of the providers reported measuring AMH levels in their patients. Some respondents measured these markers only in very young girls (e.g., 1–2 years old) or in older preteens (e.g., over 8 years old). Three out of 9 providers performed a pelvic ultrasound. In only 3/9 instances, a fertility specialist was consulted. Some physicians test for hypergonadotropism beginning after the age of 8 years [33] since FSH has been noted to be elevated in girls at an early age. The absence of the development of secondary sex characteristics is considered an indicator to initiate hormone replacement [33]. Others suggest testing serum FSH, LH and estradiol at 1 to 2 years of age and each year after the onset of puberty. Alternatively, testing may start when pubertal development is delayed. Ovarian ultrasound is recommended if there is delayed puberty, amenorrhea, or if the FSH result is elevated [32].

Hormone replacement therapy with estrogen is the mainstay of treatment of POI [33]. If secondary sexual characteristics did not develop, then estrogen therapy is administered in low, slow approach. No progesterone is added until puberty is complete, even up to 2 years. After complete breast development is achieved, then progesterone is added to reduce the risk of endometrial hyperplasia or cancer. Progesterone may be added earlier if the patient has a spontaneous menstrual bleed. There are no studies specific to hormone replacement in adolescents with galactosemia. Experience with pubertal hormone replacement has been used to guide HRT in female patients with galactosemia and POI [89, 90]. In the US, most clinicians initiate HRT between 12 and 14 years. In Europe, 40.4% of clinicians initiate treatment by age 11, 47.8% by age 13 and 7.5% wait until age 15 [90]. There is no consensus regarding the duration of HRT [88], although there have been suggestions to continue HRT until the average age of menopause [33].

Children and adults with galactosemia are at risk for low bone mass [91–96]. The pathophysiologic mechanisms leading to bone abnormalities in this population remain elusive. Surprisingly, in this disorder, there is no correlation between bone density and estradiol concentration [93]. Based on expert opinion, for prevention of osteoporosis in the pediatric population, routine assessment of bone mass has been proposed [97]. Dual-energy X-ray absorptiometry (DXA) should be performed from the age of 4 years and compared to similar age-matched controls with similar body type. Experts have

suggested that in patients with galactosemia DXA should be repeated every 2 years in patients with normal bone mineral density (BMD) and repeated yearly in patients with BMD below 0 SD [97]. If BMD is between 0 and − 1 SD, lifestyle factors such as physical activity, intake of calcium and vitamins K and D and estrogen supplementation (in girls) should be optimized. If BMD is below − 1 SD, supplementation of calcium, vitamin K (1) and vitamin D (3) has been suggested.

There are currently no known interventions that will prevent long-term complications seen in patients with classic galactosemia, including POI. Various pharmacological agents that have been suggested but lack evidence, including antioxidants, uridine, and aldose reductase inhibitors [63]. A therapeutic trial of uridine supplementation in 29 patients over 2–5 years did not significantly improve neurocognitive performance when compared to galactose-restricted diet [98]. Accumulation of galactose 1-phosphate has been attributed to causing long-term complications. Galactokinase (GALK) inhibition has been considered as a novel therapy for classic galactosemia [99]. Significant challenges remain for this potential drug, which is still being investigated.

Fertility preservation in classic galactosemia

Fertility preservation is routinely offered to patients faced with the potential to lose fertility due to gonadotoxic therapy, secondary to a diagnosis of cancer [100]. Various professional societies have developed guidelines to assist health care professionals taking care of patients faced with risk for cancer treatment related infertility [100]. With the advances made in the field of reproductive endocrinology, a range of fertility preservation techniques are available. In vitro fertilization (IVF) with embryo cryopreservation is well established. Cryopreservation of unfertilized mature oocytes is no longer considered experimental and is offered to patients [101]. Both embryo and mature oocyte cryopreservation require ovarian stimulation with injectable gonadotropins. Ovarian tissue cryopreservation and transplantation are considered experimental; however, case reports of successful pregnancies have been reported [102]. Since galactosemic patients are at high risk for POI, it is common that these patients and/or their parents might request fertility preservation, usually prior to the onset of POI. Currently, there are no recommendations for fertility preservation in this group. Some experts suggest that fertility preservation should not be offered to these patients as a common practice [103]. One reason for discouraging fertility preservation is because the pathophysiology of the process leading to ovarian damage is unknown but may be related to the galactosemia itself. Since it is unclear when the ovarian reserve declines in galactosemic patients, it is hard to know when fertility preservation should be offered. There is evidence that the insult to the ovaries may start early in life or may even be prenatal. In these early cases, fertility preservation may not be possible. The techniques are experimental in the prepubertal patient and ethical issues also arise in performing these treatments in minors [103]. Most of the girls who would benefit from fertility preservation are too young to make decisions for themselves. The only feasible option for this group of patients is ovarian tissue preservation. Even, postpubertal galactosemic women reportedly do not respond well to ovarian stimulation. Gubbels et al. reported only 1 out of 15 galactosemic patients showed a normal increase in estradiol level after ovarian stimulation with gonadotropins [54]. Although patients with galactosemia do not have severe cognitive impairment, learning disability and emotional problems have been reported and there have been questions regarding how this cognitive impairment may affect their ability to raise children or make informed decisions [103]. The counseling regarding fertility is made more complex by the fact that spontaneous pregnancies are known to occur and there is no way of predicting who will benefit from fertility preservation [103]. There is a risk of reducing fertility if one ovary is removed. The fluctuating course of this complication is highlighted by the case where ovarian preservation was performed under research protocol in a 14-year-old patient with classic galactosemia [104]. She subsequently had spontaneous pregnancies at ages 19 and 21, without the need for autografting the cryopreserved tissue. van Erven et al. [103] have published the following recommendations based on expert opinion regarding fertility preservation in classic galactosemia patients: (1) Physicians should emphasize that spontaneous pregnancies occur in women with classic galactosemia, even after POI diagnosis—though unpredictable. (2) If fertility preservation is desired, the discussion should occur early to discuss all options. (3) Cryopreservation at an early prepubertal age as a part of approved research protocol may be the best way to ensure ovarian tissue is preserved. Yet, this approach is experimental and it is not clear the future success of this approach in these patients since there is no data. (4) The ethics committee of the hospital or another independent body should review the parent's decision before the fertility preservation procedure and its use in the future. (5) Fertility preservation should be re-visited in discussion with the galactosemic patient after puberty if she is still having menstrual cycles for non-experimental fertility preservation methods (i.e., cryopreservation of eggs or embryos). Again, one needs to counsel these patients that they tend to respond to gonadotropic ovarian hyperstimulation lower than their age-matched controls. (6) Anonymous or known directed oocyte donation might be another option for classic galactosemia patients if pregnancy does not occur. Known, directed oocyte donation

may be from a family member or friend. Psychological screening and counseling for all parties involved in cases of known oocyte donation is recommended [105].

New advances in fertility preservation and restoration

Clinical and research advances in the field of fertility preservation raise exciting possibilities for patients at risk of losing their fertility. Ovarian tissue cryopreservation and human ovary autotransplantation is an experimental technique that involves ovarian tissue extraction, freezing/thawing, in vitro maturation or transplantation back into the same patient [102]. This approach is still experimental but does not require ovarian stimulation; therefore, it may be possible for prepubertal girls and young women and has the potential to restore both endocrine and reproductive ovarian functions [102]. Techniques for in vitro follicle growth where early-stage follicles retrieved by ovarian tissue extraction can be matured to functional follicles are being explored and are also experimental. Cutting-edge technologies such as the application of tissue engineering principles to bioengineer an artificial ovary [106, 107] are being studied. Similarly, in patients with premature ovarian failure, researchers are exploring in vitro activation of dormant follicles in the ovary using phosphatidylinositol-3-kinase activators and suppressing the Hippo signaling pathway and successful pregnancies have been reported [108, 109]. The prospect of utilizing ovarian stem cell-based therapeutics for ovarian regeneration also seems interesting [110]. Such advances in reproductive medicine may bring new hope to women with classic galactosemia [111].

Future directions

Newborn screening identifies galactosemia and adherence to galactose-restricted diets has markedly reduced the acute neonatal symptoms from galactosemia. The dramatic response to dietary treatment has been a success story for newborn screening. Galactosemic children now have a high survival rate; yet, the long-term outlook for these patients includes complications such as primary ovarian insufficiency and its resulting morbidity. The relative rarity of galactosemia has made it difficult to accumulate data to determine factors defining the timing of ovarian dysfunction or treatment/fertility preservation options. Some suggested future directions are:

1. More research should involve surveys of adolescents and adult women living with galactosemia to study the psychological burden caused by POI in this population and its impact on quality of life. Online survey tools and in person interviews of women with this rare disorder can be used to gain an insight into the devastating consequences of POI and the resulting infertility.
2. Reproductive specialists should be involved earlier in the care of girls and women with galactosemia. Once evidence of POI is already present, lack of available interventions makes the situation difficult. Continued support from a reproductive endocrinology and infertility specialist will improve our understanding of this complication and help patients.
3. Research should be focused on neonates and children with galactosemia. Prospective close monitoring and enrolling children in trials would advance the state of the knowledge. As this group stands to benefit from the research, they should not be excluded.
4. Women with galactosemia who are trying to conceive should be prospectively studied.
5. Long-term follow-up of patients following pregnancy and infants born to galactosemic mothers would be of interest.
6. Reproductive medicine and metabolic specialists should collaborate to advance our understanding of the role of galactose metabolism in the ovary and interventions to preserve ovarian function in this group of women.

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