ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Fertility in adult women with classic galactosemia and primary ovarian insufficiency

Britt van Erven, M.D., Ph.D.,[a] Gerard T. Berry, M.D.,[b] David Cassiman, M.D., Ph.D.,[c] Geraldine Connolly, M.D.,[d] Maria Forga, M.D.,[e] Matthias Gautschi, M.D., Ph.D.,[f] Cynthia S. Gubbels, M.D., Ph.D.,[g] Carla E. M. Hollak, M.D., Ph.D.,[h] Mirian C. Janssen, M.D., Ph.D.,[i] Ina Knerr, M.D., Ph.D.,[j] Philippe Labrune, M.D., Ph.D.,[k] Janneke G. Langendonk, M.D., Ph.D.,[l] Katrin Õunap, M.D., Ph.D.,[m] Abel Thijs, M.D., Ph.D.,[n] Rein Vos, Ph.D.,[o] Saskia B. Wortmann, M.D., Ph.D.,[p] and M. Estela Rubio-Gozalbo, M.D., Ph.D.[a]

[a] Department of Pediatrics and Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands; [b] Division of Genetics and Genomics, Manton Center for Orphan Disease Research, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; [c] Department of Gastroenterology-Hepatology, Metabolic Center, University Hospitals Leuven, Leuven, Belgium; [d] Rotunda Hospital and Temple Street Children's University Hospital, Dublin, Ireland; [e] Endocrinology and Nutrition Department, Hospital Clinic, Barcelona, Spain; [f] University Children's Hospital, Pediatric Endocrinology, Diabetes, and Metabolism, and Institute of Clinical Chemistry, Inselspital, University of Bern, Bern, Switzerland; [g] Division of Genetics and Genomics, Boston Children's Hospital/Harvard Medical School/Broad Institute of Massachusetts Institute of Technology and Harvard, Boston, Massachusetts; [h] Division of Endocrinology and Metabolism, Department of Internal Medicine, Academic Medical Center, Amsterdam, the Netherlands; [i] Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands; [j] National Centre for Inherited Metabolic Disorders, Temple Street Children's University Hospital, Dublin, Ireland; [k] Hôpital Antoine Béclère, Centre de Référence Maladies Héréditaires du Métabolisme Hépatique, Hôpitaux Universitaires Paris Sud, Clamart, France; [l] Center for Lysosomal and Metabolic Diseases, Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands; [m] Department of Clinical Genetics, United Laboratories, Tartu University Hospital, and Department of Pediatrics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia; [n] Department of Internal Medicine, VU University Medical Center, Amsterdam, the Netherlands; [o] Department of Methodology and Statistics, School for Public Health and Primary Care, Maastricht University, Maastricht, the Netherlands; and [p] Children's Hospital, Salzburger Landeskliniken and Paracelsus Medical University, Salzburg, Austria

Objective: To study pregnancy chance in adult women with classic galactosemia and primary ovarian insufficiency. Despite dietary treatment, >90% of women with classic galactosemia develop primary ovarian insufficiency, resulting in impaired fertility. For many years, chance of spontaneous conception has not been considered, leading to counseling for infertility. But an increasing number of reports on pregnancies in this group questions whether current counseling approaches are correct.

Design: Multicenter retrospective observational study.

Setting: Metabolic centers.

Patient(s): Adult women (aged >18 y) with confirmed classic galactosemia and primary ovarian insufficiency were included.

Intervention(s): Participants and medical records were consulted to obtain study data in a standardized manner with the use of a questionnaire.

Main Outcome Measure(s): Conception opportunities, time to pregnancy, pregnancy outcome, hormone replacement therapy use, fertility counseling, and the participants' vision of fertility were evaluated. Potential predictive factors for increased pregnancy chance were explored.

Result(s): Eighty-five women with classic galactosemia and primary ovarian insufficiency participated. Twenty-one women actively attempted to conceive or did not take adequate contraceptive precautions. Of these 21 women, nine became pregnant spontaneously (42.9%). This was higher than reported in primary ovarian insufficiency due to other causes (5%–10%). After a period of 12 months, a cumulative proportion of 27.8% of couples had conceived, which increased to 48.4% after 24 months and 61.3% after 27 months.

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Reprint requests: M. Estela Rubio-Gozalbo, M.D., Ph.D., Department of Pediatrics, Maastricht UMC+, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands (E-mail: estela.rubio@mumc.nl).

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Predictive factors could not be identified. A considerable miscarriage rate of 30% was observed (6 of 20 pregnancies). Although a substantial proportion of women expressed a child-wish (n = 28/53; 52.8%), the vast majority of participants (n = 43/57; 75.4%) considered conceiving to be highly unlikely, owing to negative counseling in the past.

Conclusion(s): The pregnancy rate in women with classic galactosemia and primary ovarian insufficiency was higher than for women with primary ovarian insufficiency of any cause. This shifting paradigm carries significant implications for fertility counseling and potential application of fertility preservation techniques. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)

Key Words: Classic galactosemia, GALT deficiency, primary ovarian insufficiency, fertility, pregnancy

Primary ovarian insufficiency (POI) comprises a continuum of impaired ovarian function and is an important cause of menstrual cycle disorders and fertility impairments in women (1). With its >90% prevalence in women with classic galactosemia (2), it represents the most frequent long-term complication of this inborn error of galactose metabolism. Galactose is a sugar highly important for energy delivery and glycosylation purposes, among other functions (3). The Leloir pathway constitutes the main route for galactose degradation, with one of the key enzymes being galactose-1-phosphate uridylyltransferase (GALT). Severe deficiency of this enzyme, due to mutations of the *GALT* gene, results in the metabolic disorder known as classic galactosemia, affecting ~1 in 16,000–50,000 newborns (4, 5). The disease is characterized by neonatal onset of a potentially lethal syndrome resulting in vomiting, lethargy, hepatomegaly with hepatic dysfunction, renal problems, and brain damage that quickly resolves when galactose restriction is initiated. However, despite strict dietary treatment, nearly all women develop POI with consequent reduced fertility.

The remarkably high prevalence of hypergonadotropic hypogonadism in women with classic galactosemia was first reported in 1979 (6). Meanwhile, evolved experience has shown that female patients exhibit a wide phenotypic spectrum of POI, varying from young adolescents with primary amenorrhea to individuals with normal pubertal development but irregular or absent menstrual cycles at a later stage. There seems to be a more rapid decline in the number of primordial follicles in prenatal or early postnatal life (7). Several pathophysiologic mechanisms have been postulated (8), including direct toxicity of galactose and its metabolites to oocytes and follicles, leading to accelerated atresia of the ovarian pool (9–13) and/or compromised follicle maturation (14–18). Impaired primordial germ cell development, resulting in a deficient complement of follicles, has also been indicated by animal studies (19). Furthermore, aberrant glycosylation of gene pathways (20), hormones (21), and receptors (7, 22, 23) involved in ovarian function have been suggested. Recently, dysregulation of the PI3K-Akt growth-signaling pathway has been implicated as well, which might affect oocyte development (24). Moreover, disease models have shown evidence for oxidative stress, endoplasmic reticulum stress, and activation of the unfolded protein response pathway in classic galactosemia (25–29). The hypothesis of a prenatal or early postnatal origin of the ovarian damage is supported by the consistently reduced concentrations of antimüllerian hormone and elevated gonadotropin concentrations that can be found in these girls already at an early age (30, 31).

In women with POI of any cause, pregnancies are not excluded, owing to the varying and unpredictable course of impaired ovarian function that POI reflects (1), and in general 5%–10% conceive spontaneously (32). Also in women with classic galactosemia, spontaneous pregnancies have been reported regularly despite the presence of POI (4,5,33–37). Only one study in a small number of patients (n = 22) has addressed pregnancy attempts in women with classic galactosemia and concluded that most women did not try to become pregnant because they had been told they could not have children (33). Interestingly, of the few women who attempted to conceive spontaneously (n = 9), as many as four (44%) succeeded.

These data lead to the question of whether the pregnancy rate for this population might be higher than for women with POI due to other causes. Further exploration of pregnancy rates in this specific group is crucial to improve counseling of young patients and their parents. Furthermore, increased insight is essential for accurate assessment of the potential value of fertility preservation techniques (38). The present international epidemiologic study investigated fertility in a cohort of adult women with classic galactosemia and POI to determine whether current reproduction counseling of patients and their families is accurate.

METHODS

Study Design and Participants

This observational study was conducted in 15 metabolic centers in the Netherlands, Austria, Belgium, Estonia, France, Ireland, Spain, Switzerland, and the United States. Centers and patients were informed about this study through the international Galactosemia Network (www.galactosemianetwork.org) and patient associations, respectively. Patients' participation and informed consent were solicited during gatherings of patient associations, at the outpatient clinic, or by telephone if a patient had participated in an earlier study and had given consent to be recontacted. Participants were enrolled from February 2014 to July 2016. We obtained ethics approval for this study from local Research Ethics Committees in the participating centers. Informed consents were obtained.

Adult women (≥18 years of age) with classic galactosemia and POI were invited to participate in the study. Classic galactosemia diagnosis was confirmed by means of GALT enzyme activity assay and/or *GALT* mutation analysis. POI