



Pregnancies and associated events in women receiving  
Enzyme Replacement Therapy for late onset Glycogen  
Storage Disease Type II (Pompe disease)

Journal:	The Journal of Obstetrics and Gynaecology Research
Manuscript ID	JOGR-2015-0859.R2
Manuscript Type:	Original Manuscript
Date Submitted by the Author:	15-Mar-2016
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Keywords:	2.210 General Genetics < 2.200 Obstetrics: Genetics and Teratology < 2 Obstetrics, 2.720 Prepregnancy Counseling < 2.700 Obstetrics: Diagnosis and Management < 2 Obstetrics, 2.719 Prenatal Care < 2.700 Obstetrics: Diagnosis and Management < 2 Obstetrics

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The Journal of Obstetrics and Gynaecology Research

1 Title:

2 Pregnancies and associated events in women receiving Enzyme Replacement Therapy for  
3 late onset Glycogen Storage Disease Type II (Pompe disease)

4

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23 Word count summary: 219 words

24 Word count text: 3491 words

25 Number of figures and tables: 3 tables

26

27 Abstract:

28 Aim: Glycogen Storage Disease Type II (GSD II or Pompe disease; OMIM; 232300) is a  
29 rare autosomal recessive lysosomal storage disorder resulting from deficiency of alpha  
30 glucosidase and accumulation of glycogen in muscle. Clinical symptoms include weakness  
31 of skeletal and respiratory muscles and in infants, cardiomyopathy. Patients with GSD II  
32 receive infusions of recombinant alpha glucosidase (enzyme replacement therapy; ERT),  
33 which slow progression of disease. ERT is given to males and females of all ages but as yet  
34 little is documented around the effects of continuing ERT during pregnancy. The objective  
35 of this case series was to ascertain the pregnancy outcomes of women with GSD II on ERT  
36 and to describe and adverse events associated with pregnancy, delivery and therapy.

37 Methods: The medical records of 8 women attending the Royal Free Hospital Lysosomal  
38 Storage Disorders Unit were reviewed. Four of the eight women experienced 7  
39 pregnancies over a period of 8 years.

40 Results: In this series GSD II was associated with interventional deliveries but normal  
41 neonates. Cessation of ERT in early pregnancy resulted in deterioration of maternal  
42 symptoms and emergence of allergic reactions on restarting ERT.

43 Conclusion: Individualised care plans for patients are required to ensure the best neonatal  
44 and maternal outcomes. Consideration should be given to the potential benefits to mother  
45 and fetus of continuing ERT during pregnancy.

46

47 Key words: Glycogen Storage Disease Type II (GSD II), recombinant alpha glucosidase  
48 Enzyme Replacement Therapy (ERT), pregnancy, infusion reaction.

49

50

51 Introduction:

52 Glycogen Storage Disease Type II is a rare, autosomal recessive disorder of glycogen  
53 metabolism.<sup>1</sup> Mutations in the gene encoding the enzyme acid alpha-glucosidase (GAA),  
54 an enzyme which converts glycogen into glucose within lysosomes as part of  
55 glycogenolysis, result in reduced or absent GAA activity.<sup>1</sup> Patients with GAA mutations  
56 are not able to complete this process resulting in excess lysosomal glycogen. The  
57 accumulation of glycogen within muscle overtime changes the muscle structure and  
58 subsequently function. These changes are seen most commonly within the cardiac and  
59 skeletal muscles with resultant clinical manifestations.<sup>2</sup> Late onset GSD II is usually milder  
60 in presentation compared with the infantile onset form<sup>2</sup>, with infantile onset of disease often  
61 progressing rapidly. Most adults with late onset GSD II will experience progressive muscle  
62 weakness (most commonly proximal, respiratory and trunk muscles).<sup>2</sup> In the context of late  
63 onset disease and relatively slow progression, patients reach reproductive age resulting in a  
64 different set of challenges to management of infantile Pompe disease. The balance between  
65 managing maternal symptoms and fetal safety may be difficult, especially due to the lack of  
66 availability of data with regard to managing enzyme replacement in these patients while  
67 pregnant.

68 Enzyme replacement therapy (Alglucosidse alfa, Myzome®, Genzyme Sanofi) has been  
69 available in the United Kingdom since 2006. Little is documented of effects during  
70 pregnancy and the risk/benefit balance of continuing therapy during pregnancy is evaluated  
71 on an individual basis. No prescribing guidelines are available from manufactures when  
72 considering continuing or re-starting enzyme replacement in pregnancy<sup>3</sup>.

73

74 Methods:

75 The medical records of the eight women with Pompe disease known to the lysosomal  
76 storage disorders unit of the Royal Free London NHS Foundation Trust were surveyed for  
77 information about the use of enzyme replacement therapy during pregnancy and the  
78 subsequent maternal and neonatal outcomes as a non-IRB quality improvement project.  
79 All Pompe patients had confirmed diagnosis on basis of alpha glucosidase activity and  
80 genotyping. Four of the eight patients were found to have experienced seven pregnancies  
81 since their referral to the unit, after diagnosis and after introduction of ERT in 2006.  
82 Verbal consent was obtained from the patients for this case series and all encounters were  
83 at the Lysosomal Storage Disorders Unit (a designated centre for management of lysosomal  
84 storage disorders including Pompe disease) of The Royal Free NHS Foundation Trust, a  
85 National Health Service (NHS) hospital in the United Kingdom. A total of four patients  
86 became pregnant over a time period of eight years (2006–2015), with all four patients being  
87 on regular routine enzyme replacement therapy around the time of conception. Prior to  
88 conception all patients were reviewed and examined neurologically every 6 months by  
89 consultant physicians in the lysosomal storage disorders unit, dieticians and  
90 physiotherapists. After conception, the same standard of care continued with the addition of  
91 obstetric and if appropriate, anaesthetic consultant input. The case histories were reviewed  
92 by an obstetrician and a metabolic physician. In addition patients were contacted to provide  
93 further detail in regard to their obstetric histories.

94

95 Results:

96 Since the introduction of enzyme replacement for Pompe disease in the UK there have  
97 been seven pregnancies in four women with Glycogen Storage Disease Type II attending

98 the Royal Free NHS Foundation Trust Lysosomal Storage Disorders Unit. Of the  
99 pregnancies, six resulted in live births, and one terminated electively. Detailed parameters  
100 around the 7 pregnancies are given in table 2.

101

102 Preconception:

103 Symptoms prior to diagnosis included non-specific decreased effort tolerance, lower  
104 back pain, non-specific whole body pain and intermittent diarrhoea. Muscle power at  
105 diagnosis varied between full power at diagnosis, mild loss of proximal muscle power  
106 moderate loss of proximal upper limb power and lower limb power, and more severe  
107 loss of proximal muscle strength.

108 Baseline lung function and sleep study tests were normal for three out of the four  
109 patients. The remaining patient had moderately-severe decreased respiratory function  
110 demonstrated on spirometry and confirmed type 2 respiratory which resolved with  
111 home nocturnal BiPAP. All patients had normal cardiac function at diagnosis. During  
112 pregnancy patients received dietary advice including food safety, use of high protein  
113 diet, folic acid, vitamin D, and avoidance of vitamin A supplements and limitation to  
114 no more than two portion of oily fish per week.

115

116 Enzyme replacement therapy adjustments during the pregnancies:

117 The time period between diagnosis and commencing ERT was between 2 and 6  
118 months (mean 4.1 months). The mean time from starting ERT to pregnancy was  
119 (22.75 months – range 8 months 2 weeks to 3 years 2 weeks. While on ERT three of  
120 the patients conceived for the first time while the remaining patient conceived for the

121 fourth time. Three of the patients went on to have second pregnancies while on ERT  
122 (two patients becoming pregnant for the second time and one patient becoming  
123 pregnant for the fifth time). Enzyme replacement therapy was stopped in the first  
124 trimester in all four patients. During the first pregnancy, while off therapy, only one  
125 of the four patients did not experience any subjective or objective muscle strength  
126 decline (patient 1 in table 2). Patient 1 became pregnant twice while on ERT and her  
127 muscle strength remained unchanged throughout. The other three patients  
128 experienced varying degrees of muscle strength decline as outlined below. ERT was  
129 re-started in the post-partum period in five out of the seven pregnancies, and at  
130 gestations of 16/40 and 29/40 in the remaining two pregnancies. Factors influencing  
131 the decisions to restart ERT were mostly dictated by the progression of symptoms off  
132 ERT and patient choice.

133

134 Individual Courses during pregnancy:

135 Patient 1 had three pregnancies and deliveries prior to diagnosis and the start of  
136 this review. All deliveries were unassisted at 42/40, term and 39/40 respectively. There  
137 were no postpartum or foetal complications. All three deliveries were at secondary  
138 care maternity units. During both subsequent pregnancies after diagnosis of Pompe  
139 disease, patient 1 stopped enzyme replacement during the first trimester and re-  
140 started postpartum (at 6 weeks postpartum and 5 weeks 4 days postpartum  
141 respectively). Muscle strength and lung function remained stable during both  
142 pregnancies. She had a normal vaginal delivery (NVD) at 41 weeks in the first  
143 pregnancy and C-section for breech postdates at 42 weeks in the second.

144 Patient 2, who stopped ERT in the 8<sup>th</sup> week of pregnancy, developed objective  
145 proximal and distal muscle weakness while pregnant (upper limb power 4/5 □ 3+/5,  
146 lower limb 3+/5 □ 3/5). After this otherwise uneventful pregnancy delivered by NVD  
147 at 40+2 weeks she had concerns about a second pregnancy in light of her potentially  
148 progressive disease and opted for an elective termination of pregnancy in the first  
149 trimester. She developed subjective shortness of breath in this pregnancy; however  
150 her lung function tests remained normal. She did not stop ERT during this time.

151 In her first pregnancy patient 3 developed isolated proximal lower limb weakness  
152 (MRC 4/5 □ 3/5) after stopping enzyme in the first trimester and this improved upon  
153 restarting ERT at 29 weeks. She also developed subjective shortness of breath (with  
154 lung function tests remaining normal), an episode of first trimester vaginal bleeding  
155 (6/40), and nausea. She had an elective C-section at 37+5 weeks. During her second  
156 pregnancy while off ERT from 5 weeks, patient 3 again developed muscle weakness,  
157 this time more severe than the previous pregnancy. (Decrease in proximal muscle  
158 power – hip adductors 3/5 □ 2/5, hip adductors 3/5 □ 2/5, knee 3/5 □ 2/5). Upper limb  
159 muscle strength remained stable. She also developed objective decline in respiratory  
160 function (FEV1 73% predicted and FVC 68% predicted) while not of ERT. This  
161 pregnancy was also complicated by second trimester vaginal bleeding (27+1/40) which  
162 resolved spontaneously without complication, hyperemesis gravidarum, (which  
163 resolved at 15/40), a right swollen leg, shortness of breath at rest and associated chest  
164 pain at 30+2/40. She was treated empirically with low molecular weight heparin until  
165 investigations confirmed the absence of a thromboemolism. She also developed an  
166 irritable uterus at 33+/40 with associated abdominal pain. This was managed  
167 conservatively and resolved without complication. She underwent a C-section at 36+2  
168 weeks and recommenced ERT at 13days post-partum.



169 Patient 4, who stopped ERT at 6 weeks gestation, developed progressive weakness of  
170 both shoulder and hip muscles (MRC 4+/5 □ 4/5 and MRC 2+/5 □ 2/5 respectively).  
171 She had been found to have decreased FVC (48% predicted) and FEV1 (55%  
172 predicted), and confirmed type 2 respiratory failure at diagnosis. Despite initial  
173 respiratory compromise at diagnosis, this remained stable during pregnancy and sleep  
174 studies done at 17 and 34 weeks were both normal. She recommenced ERT at 16  
175 weeks and had a ventouse delivery at 42 weeks.

176

177 No patient had invasive prenatal testing. All patients were offered genetic counselling.

178

179 Labour and delivery:

180 Delivery was by spontaneous vaginal delivery for two out of the six pregnancies, and  
181 operative vaginal delivery (ventouse) for one of the six pregnancies, which were  
182 allowed to continue. The operative vaginal delivery was done in the second stage of  
183 labour. This patient's birth plan (designed by a specialist obstetrician in a secondary  
184 level maternity unit) involved allowing her to labour spontaneously (with epidural  
185 anaesthetic) but aimed to limit the second stage to 30 minutes to prevent maternal  
186 exhaustion. 45 minutes into the second stage of labour she was delivered without  
187 complication. All three Caesarean sections were done electively or semi-electively.  
188 Reasons for Caesarean section included breech presentation in patient 1, elective and  
189 brought forward in patient 3 in the context of confirmed fetal intrauterine growth  
190 retardation (IUGR) (Grade 3 emergency Caesarean section), previous Caesarean  
191 section in patient 3 and. No post-partum complications were documented, regardless

192 of mode of delivery, and in particular there were no post-partum haemorrhages  
193 suggesting uterine muscle function was appropriate after delivery in all cases.

194

195 Reactions to enzyme replacement therapy:

196 Two of the four patients had documented and repeated reactions to the ERT (Alglucosidse  
197 alfa) after restarting ERT postpartum. Patient 2 in (table 3) had her first reaction 2 years  
198 and 9 months after the first Alglucosidse alfa infusion. Her first allergic type reaction  
199 occurred while receiving an infusion at home and was comprised of skin and respiratory  
200 manifestations (hives, pruritus, tightness in the chest and throat). The first episode resolved  
201 with symptomatic management (Hydrocortisone and Chlorpheniramine). This patient  
202 continued to have multiple reactions relating to the infusions – symptoms were varied and  
203 included rash, shortness of breath, tightness around chest and throat, vague abdominal pain  
204 and itching all requiring symptomatic intervention (Salbutamol, Hydrocortisone and  
205 Chlorpheniramine). During two separate reactions, this patient developed cardiovascular  
206 involvement as a result of the infusions (low blood pressure and both episodes requiring IV  
207 fluid responsive to stat boluses). One episode was accompanied by anaphylaxis □  
208 unrecordable blood pressure, shortness of breath and decrease in oxygen saturations. This  
209 episode required 2 doses of IM adrenaline and fluid resuscitation. After the anaphylactic  
210 episode, the enzyme replacement infusions were stopped for 8 weeks. Positive IgG  
211 antibodies to Alglucosidse alfa were confirmed at a titre of 3200. 8 weeks after the last  
212 anaphylaxis episode, a desensitisation programme was commenced as an inpatient. This  
213 involved initially receiving 1:100<sup>th</sup> of her previous dose and increasing doses incrementally  
214 on a weekly basis over a period of three months. This patient had remained off ERT  
215 throughout the entire pregnancy after the pregnancy was confirmed (at 8+1/40 gestation).  
216 The first treatment interruption was 3 years 2 weeks after initially starting treatment and

217 enzyme therapy was re-initiated 2 months post-partum. After desensitisation, most of the  
218 infusions remained uneventful with only 2 episodes of mild pruritus, which responded to  
219 symptomatic management.

220 Patient 3 developed a first infusion related reaction 4 years and 2 months after her first  
221 infusion. IgG antibodies to Alglucosidse alfa were positive (titre of 1600) 2 years prior to  
222 the first reaction. This patient had her first break in enzyme replacement therapy 2 years 4  
223 months after starting treatment (1<sup>st</sup> trimester of her first pregnancy). ERT was restarted at  
224 29/40 gestation in her first pregnancy and in the post-partum period in her second  
225 pregnancy. No desensitization was required after stopping therapy the first time however in  
226 light of the previous reactions and extended time off treatment, ERT was restarted  
227 incrementally postpartum without complication after the second pregnancy.

228

#### 229 Discussion:

230 Patients with Glycogen Storage Disease Type II are reviewed on an individual basis prior to  
231 starting ERT. Inclusion criteria for starting treatment according to NHS England standard  
232 operating procedures include: the confirmation of definitive diagnosis (enzymatic or  
233 genetic), muscle weakness and or respiratory compromise, impaired quality of life as a  
234 result of symptoms and commitment to follow the recommended protocols for attending  
235 treatment session and monitoring subsequent response.<sup>2</sup> Alglucosidse alfa has been  
236 developed as a recombinant human acid  $\alpha$ -glucosidase as enzyme replacement therapy for  
237 patients with Glycogen Storage Disease Type II. It is hoped that the enzyme replacement  
238 will restore enzymatic activity<sup>4</sup>, deplete accumulated substrate, prevent further  
239 accumulation and allow for repair of damaged myocytes<sup>3</sup>. Alglucosidse alfa for use in  
240 pregnancy is categorised as class B according to the prescribing information and class C by

241 the FDA (Food and drug administration. According to the package insert<sup>3</sup>, reproductive  
242 studies performed in pregnant mice and rabbits at an intravenous doses of 40mg/kg/day  
243 (double dose than recommended use in humans), revealed no evidence of reduced fertility  
244 or harm to the foetus as a result of Myzome®<sup>3</sup>. There are, however, no adequate and well-  
245 controlled studies in pregnant women. Therefore with the available data, the balance  
246 between maternal symptom control, prevention of disease progression (as a result of  
247 treatment interruption) and fetal safety need to be balanced in order to ensure the best  
248 possible maternal and foetal outcomes.

249 In our recent clinical practice ERT was stopped after discussion with the women in  
250 regard to the risk benefit ratio out of caution during the first trimester with the intention of  
251 restarting after organogenesis. However, personal preference amongst patients led to delay  
252 in re-initiation in two women. Stopping treatment, as demonstrated above, resulted in three  
253 of the four patients developing subjective and objective decline in muscle function during  
254 pregnancy. This deterioration of function, with its associated physical and psychological  
255 consequences, requires balanced assessment. In addition to the assessment of functional  
256 decline while not on ERT, patient preference need to be considered. One patient (patient 2)  
257 decided to delay restarting ERT to the post-partum period out of choice. This decision was  
258 influenced by the occurrence of IUGR in her sisters' pregnancy (patient 3). No one cause  
259 could be confidently attributed to the IUGR although recognisable risk factors, including  
260 smoking, were present. Despite marked decline in muscle strength and lung function,  
261 patient 3 elected not to restart therapy during her second pregnancy. This preference was  
262 largely influenced by the presence of previous allergic reactions to ERT upon restarting.

263 Anti-drug antibodies, and in some cases clinical reactions, to Alglucosidase alfa are well-  
264 recognised side effects of ERT<sup>3</sup>. The two women who developed anti-drug antibodies and  
265 infusion reactions on restarting ERT after pregnancy had a varying response to ongoing

266 Alglucosidase alfa infusions. After patient 2 developed anaphylaxis requiring adrenalin and  
267 emergency supportive care, she was successfully desensitized using a graded regime which  
268 has had a good outcome. No further anaphylactic reactions have occurred however she does  
269 require intermittent symptomatic treatment during some infusions. Patient 3 was  
270 successfully desensitized and restarted on ERT after her second pregnancy.

271 After analysis of the progression of these four women through seven pregnancies,  
272 outcomes in women with Glycogen Storage Disease Type II and the foetus can be good.

273 No definitive recommendation can be made on the use of ERT throughout pregnancy  
274 and the relative risks and benefits should be discussed individually with the LSD physician  
275 and patient. This should take into account the likelihood of deterioration in respiratory and  
276 muscle function off ERT, the possibility of reactions on recommencing and the view that  
277 the health of the baby is well served by preserving the health of the mother in pregnancy.  
278 There are however some issues which may benefit from particular attention.

279 We suggest the following considerations for management during pregnancy:

280

281 Pre-conception:

282 Upon diagnosis all patients should be reviewed for appropriateness of starting ERT.  
283 Baseline investigations (routine bloods, neurological assessment, lung and cardiac function  
284 tests and if clinically indicated, a sleep study) should all be done prior to starting enzyme  
285 replacement therapy<sup>2</sup>. These should be repeated prior to conception to allow for meaningful  
286 comparison should symptoms improve or worsen. Routine monitoring for non-pregnant  
287 patients with Glycogen Storage Disease Type II ideally should include outpatient follow up  
288 every six months <sup>2</sup>(during which symptom monitoring, nutritional assessment and repeat  
289 blood tests are all routinely done). Lung function tests and bone health assessments should

290 be performed annually (or more frequently if clinically indicated). Sleep studies,  
291 echocardiograms and more extensive investigations should be done as clinically  
292 indicated. Disease stabilisation would be preferable prior to conception. In light of the  
293 autosomal recessive nature of inheritance, in non-consanguineous families the risk of  
294 offspring developing the disease is low, however genetic counselling should be offered to  
295 all patients ideally prior to conception.<sup>5</sup> Other medications may require alteration to more  
296 'pregnancy safe' alternatives, if they are potentially teratogenic. (Particular attention  
297 should be paid to regular analgesia, which patients with GSD II frequently require). As in  
298 all pre-natal care, exploration around potentially harmful social habits also require  
299 addressing. Decisions to proceed with any pregnancy ultimately lie with the patient and  
300 extensive information, counselling and support should be made available to all pregnant  
301 women with GSD II.

302

303 During pregnancy:

304 In addition to routine obstetric care, the women with GSD II should be seen at least once  
305 every trimester by a specialist Lysosomal Storage Disorders (LSD) team. Anaesthetic input  
306 should be arranged early with local or regional anaesthesia discussed as being the  
307 techniques of choice, while bearing in mind muscular skeletal abnormalities may make this  
308 difficult.<sup>9</sup> Discussions about mode of delivery and available options should be highlighted  
309 to the women, with patient involvement in the development of birth plans. All  
310 investigations (baseline and subsequent) should made available to obstetrics, neurology and  
311 anaesthetic colleagues prior to assessment and birth planning consultations. Input by  
312 obstetric, neurology, respiratory, anaesthetic and dietician specialists (in addition to  
313 metabolic consultant specialist input) should be determined on an individual case basis

314 depending on baseline and progressive symptoms, severity of disease and previous obstetric  
315 history. All patients should be reviewed by a specialist dietician.

316 Consideration should be given to continuing ERT during pregnancy to avoid  
317 neuromuscular decline however if ERT is stopped and restarted monitoring should be  
318 performed during infusions for allergic reactions occurring after therapy interruption.  
319 Adjustments in body weight need to be considered, as the dose of the therapy will require  
320 titration accordingly. Despite multiple physiological changes which occur in pregnancy, the  
321 respiratory flow rates (FEV1 and PEFr) are mostly unchanged in normal pregnancies<sup>6</sup>.  
322 However while not on ERT women may be at risk of respiratory muscle functional  
323 decline<sup>7</sup>. Special attention to ongoing monitoring of respiratory function is essential with  
324 the addition of investigations such as a sleep study if clinically indicated (with attention to  
325 signs such as early morning headaches). For all women, whether on ERT during pregnancy  
326 or not, symptoms of worsening disease progression should be carefully graded and  
327 deterioration in function minimised with the assistance of physiotherapy and by restricting  
328 the duration without ERT on consideration and discussion of the relative risks and benefits.

329

330 During labour:

331 As pregnancy progresses and nears delivery, significant metabolic stress is present<sup>8</sup>.  
332 Avoiding maternal fatigue is a key consideration. Recognising that women with GSD II  
333 may tire more easily is a key consideration and they may benefit from early intervention<sup>8</sup>.  
334 For example, consideration should perhaps be given to a limited length of active second  
335 stage (pushing) with an elective assisted vaginal delivery planned, if delivery not imminent  
336 within a specified time period (as in patient 4's case). This should be reviewed on an  
337 individual case basis. Caesarean should only be indicated for either routine obstetric

338 reasons or medical reasons relating to GSD II and clinical condition around the time of  
339 delivery. Addressing maternal pain and anxiety early and having clear objectives for the  
340 birth plan are considered desirable.

341

342 Postpartum:

343 All women should be reviewed by the LSD team in the postpartum period. Re□  
344 commencement of ERT if initiated is appropriate. Full neurological assessment should be  
345 performed on the first clinical visit through to the postpartum period to quantify and  
346 identify any symptoms which worsened during this time. Care should be taken to ensure  
347 that patients are monitored for new onset adverse/allergic reactions to ERT on re□  
348 commencement of the drug. Patients should receive advice from occupational and  
349 physiotherapists with respect to the safe use of baby slings, prams and buggies and lifting.

350

351 Neonatal review should be as per routine protocol by the paediatric team, paying special  
352 attention to development and growth.

353

354 Breast feeding

355 No adverse effects to breastfed infants from mothers on ERT have been noted so far,  
356 however no information is available around the safety of ERT while breastfeeding. If  
357 preferred, the mother may use previously expressed milk during the 24 hours after the last  
358 infusion and discard expressed milk during this time. Patients are encouraged to participate  
359 in prospective data collection.

360



361 Summary:

362 Women with Glycogen Storage Disease Type II do appear to have identifiable issues  
363 related to pregnancy. Decline in muscle function while stopping ERT was the most  
364 noticeable and prevalent finding, suggesting consideration should be given to continuing  
365 ERT or its early re-initiation. ERT infusion reactions, possibly linked to therapy  
366 interruptions, can be overcome with a combination of symptomatic control and/or graded  
367 desensitisation. In this series, there was a high Caesarean section rate. There were no  
368 congenital abnormalities and all of the neonates were born in good condition, although 2  
369 out of 6 babies were born with birth weights less than 10<sup>th</sup> centile for sex and gestation. It is  
370 recognised from this series that challenges exist around the administration of ERT to  
371 women with Glycogen Storage Disease Type II in pregnancy, however, with individual  
372 patient care plans, overall outcomes for both mother and foetus can be favourable.

373 Acknowledgements:

374 We thank the patients and their families for their assistance with this study

375 Disclosures:

376 Mrs L. Richfield has received honoraria for speaking and production of patient information  
377 sheet from Genzyme.

378 Dr Hughes has received honoraria for speaking and advisory boards and support for travel  
379 from Genzyme/Sanofi.

380 The other authors have no disclosures.

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The Journal of Obstetrics and Gynaecology Research

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Table 1: Baseline Information

	Patient 1	Patient 2	Patient 3	Patient 4
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Age at diagnosis (Years)	29	16	13	31
Alpha glucosidase (acabose assay)	1.5	0.15	0.13	2.6
Mutation	c.132113G>T c.1114C>T	c.1239C>G c.2228A>G	c.1239C>G c.2228A>G	c.132113G>T c.525delT
Muscle function at diagnosis	Proximal muscle weakness (MRC 4/5 UL+LL)	Proximal muscle weakness (MRC 4/5 UL, 3+/5 LL)	Full power at diagnosis	Proximal muscle weakness (MRC 4+/5 UL, 2+/5 LL)
Lung function at diagnosis	Normal	Normal	Normal	FVC (48% predicted), Decreased FEV1 (55% predicted), FEV1/FVC ratio 110%
Cardiac function at diagnosis	Normal	Normal	Normal	Normal
Sleep study at diagnosis	Not documented	Normal	Normal	Confirmed type two respiratory failure (high arterial CO <sub>2</sub> )
G/P at diagnosis (prior to ERT)	G3/P3	G0/P0	G0/P0	G0/P0
Time ERT started after diagnosis	3/12	2/12	5.5/12	6/12
Period from first starting ERT to pregnancy	18/12	3 years 2 weeks	2 years 4 months	8.5/12

415 G/P – Gravidity/Parity, ERT – Enzyme Replacement Therapy

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433 Table 2: Pregnancy information

	Patient 1	Patient 2	Patient 3	Patient 4
First pregnancy since starting ERT				
G/P while on ERT after pregnancy confirmed	G4/P3	G1/P0	G1/P0	G1/P0
Social habits during pregnancy	Nil	Abstained from smoking	Continued to smoke	Nil
Gestation at which ERT stopped (weeks +days)	3	8+1	Unknown (in 1st trimester)	6
Gestation or Time post-partum ERT restarted	6 weeks post partum	8 weeks post partum	29 weeks gestation	16 weeks gestation
Symptoms while pregnant and not on ERT	Muscle Power:			
	No change	Decline in power. Proximal LL MRC 3+/5 □ 3/5, UL 4/5 □ 3+/5.	Decline in power. UL strength remained unchanged. Proximal LL MRC 4/5 □ 3/5.	Decline in power. (Proximal UL MRC 4+/5 □ 4/5 LL MRC 2+/5 □ 2/5
	Lung function:			
	Unchanged	Unchanged.	Subjective breathlessness – remained unchanged.	Unchanged.
	Other:			
	Increase in early morning headaches (sleep study normal).	Nil	Calf pain, unexpected falls.	Non-specific increase in muscle aches. 2xsleep studies (17/40, 34/40 remained stable).
Complications during pregnancy	Nil	Nil	Threatened miscarriage at +/□ 6/40 – resolved without complication.	First trimester nausea (resolved by 10/40)
Complications/interventions during labour	Nil	Nil	Nil	Operative delivery
Gestation at delivery	41	40+2	37+5	42
Method of delivery	Normal Vaginal Delivery	Normal Vaginal Delivery	Elective C/section	Operative Vaginal Delivery (Ventouse)
	Patient 1	Patient 2	Patient 3	Patient 4
Indication for C/Section or operative vaginal delivery	N/A	N/A	Elective (Early due to confirmed IUGR)	Elective to prevent maternal exhaustion
Birth weight	3969 grams	2660 grams	2540 grams	3657 grams
Percentile for sex and gestation at birth	Between 75 <sup>th</sup> –91 <sup>st</sup> centile	Below 9 <sup>th</sup> centile	Below 9 <sup>th</sup> centile	Between 50 <sup>th</sup> –75 <sup>th</sup> centile
Apgar score	Unknown	9 and 10	9 and 10	8 and 10
Neonatal complications	Nil	Nil	IUGR with low birth.	Nil

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	Patient 1	Patient 2	Patient 3	Patient 4
<b>Second Pregnancy since starting ERT</b>				
G/P while on ERT after pregnancy confirmed pregnant	G5/P4	G2/P1	G2/P1	
Social Habits during pregnancy	Nil	Continued to smoke	Continued to smoke	
Gestation at which ERT was stopped (weeks)	7	Not stopped	5	
Time post-partum ERT was restarted	5 weeks post partum	N/A	13 days post partum	
Symptoms while pregnant and not on ERT	<b>Muscle power</b>			
	No change	No change	Decline in power. UL remained unchanged. Proximal LL 4/5 □ 3/5, hip adductors 3/5 □ 1/5, hip adductors 3/5 □ 2/5, knee 3/5 □ 2/5.	
	<b>Lung function</b>			
	Unchanged	Subjective shortness of breath	Subjective and objective decline – at 34/40 FEV1 73% predicted, FVC 68% predicted.	
Complications during pregnancy	<b>Other:</b>			
	Nil	Nil	Early morning headaches (sleep study normal)	
	Breech presentation	Elective TOP – patient choice.	1. Hyperemesis episode at 15/40 2. Threatened miscarriage at 27+1/40 3. Suspected DVT at 30+2/40 – excluded on ultrasound 4. Irritable uterus at 33+6	
Complications/interventions during labour	Nil	N/A	Nil	
Gestation at delivery (weeks + days)	42	N/A	36+2	
Method of delivery	C/Section	N/A	C/Section	
Indication for C/Section	Breech presentation & post dates	N/A	Previous C/Section	
Birth weight	4026 grams	N/A	2476 grams	
Percentile for sex and gestation at birth	75 □ 91 <sup>st</sup> centile	N/A	Between 25 <sup>th</sup> □ 50 <sup>th</sup> centile	
Apgar score	Unknown	N/A	9 and 10	
Neonatal complications	Nil documented	N/A	Nil documented	

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G/P – Gravidity/Parity, ERT – Enzyme Replacement Therapy, UL □ Upper Limb, LL □ Lower Limb

437 Table 3: Reactions to ERT

Antibody response to ERT				
	Patient 1	Patient 2	Patient 3	Patient 4
First episode	N/A	2 years 9 months after first infusion	4 years 2 months after first infusion	N/A
Symptoms of reaction	N/A	Whole body itching, hives type rash, shortness of breath, wheeze, 1 episode of anaphylaxis reaction requiring adrenalin.	Whole body itching.	N/A
Antibody confirmed	N/A	IgG positive 3200 Titre	IgG positive 1600 Titre	N/A

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