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Title:

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

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Abstract:

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

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

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

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

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

Introduction:

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

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

Methods:

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

Results:

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

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

Preconception:

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

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

Enzyme replacement therapy adjustments during the pregnancies:

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

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

Individual Courses during pregnancy:

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

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

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

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

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

Labour and delivery:

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

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

Reactions to enzyme replacement therapy:

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

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

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

Discussion:

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

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

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

Anti-drug antibodies, and in some cases clinical reactions, to Alglucosidse alfa are well-recognised side effects of ERT[3]. The two women who developed anti-drug antibodies and infusion reactions on restarting ERT after pregnancy had a varying response to ongoing

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

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

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

We suggest the following considerations for management during pregnancy:

Pre-conception:

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

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

During pregnancy:

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

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

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

During labour:

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

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

Postpartum:

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

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

Breast feeding

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

Summary:

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

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Table 1: Baseline Information

	Patient 1	Patient 2	Patient 3	Patient 4

Age at diagnosis (Years)	29	16	13	31
Alpha glusodase (acabose assay)	1.5	0.15	0.13	2.6
Mutation	c.□32□13G>T c.1114C>T	c.1239C>G c.2228A>G	c.1239C>G c.2228A>G	c.□32□13G>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 CO2)
G/P at diagnosis (prior to ERT)	G3/P3	G0/P0	G0/PO	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

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

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□91st centile	Below 9th centile	Below 9th centile	Between 50th □75th centile
Apgar score	Unknown	9 and 10	9 and 10	8 and 10
Neonatal complications	Nil	Nil	IUGR with low birth.	Nil

434

435

	Patient 1	Patient 2	Patient 3	Patient 4
Second Pregnancy since starting ERT				
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		Muscle power		
	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.	
		Lung function		
	Unchanged	Subjective shortness of breath	Subjective and objective decline – at 34/40 FEV1 73% predicted, FVC 68% predicted.	
		Other:		
	Nil	Nil	Early morning headaches (sleep study normal)	
Complications during pregnancy	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□91st centile	N/A	Between 25th□50th centile	
Apgar score	Unknown	N/A	9 and 10	
Neonatal complications	Nil documented	N/A	Nil documented	

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

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

ERT – Enzyme Replacement Therapy