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Case Report

Pregnancy in patients with mucopolysaccharidosis: a case series

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ABSTRACT

The mucopolysaccharidoses (MPS disorders) are rare inherited diseases associated with multi-organ accumulation of glycosaminoglycans, leading to musculoskeletal, respiratory, cardiac, neurological, ophthalmological, otolaryngological, and gastrointestinal abnormalities. As a result of improvements in diagnosis, multi-disciplinary care, and therapies such as enzyme replacement therapy and hematopoietic stem cell transplantation, an increasing number of patients with MPS are reaching adulthood and are involved in family planning. Data on fertility and pregnancy outcome in MPS is sparse and comprises primarily isolated case reports. To address this evidence gap, we present a case series on fertility and pregnancy in eight mothers and five fathers with MPS. This case series demonstrates that women with MPS have high-risk pregnancies and deliveries secondary to their underlying disease. However, with appropriate pre-conceptual multi-disciplinary evaluation, optimization and discussion regarding potential risks, combined with regular multi-disciplinary maternal and fetal surveillance in a tertiary center, the outcome of most pregnancies in this case series seems to be favorable with all babies developing normally. Partners of fathers with MPS had uncomplicated pregnancies and deliveries. All children were healthy, with normal growth and development.

1. Introduction

The mucopolysaccharidoses (MPS disorders) are rare inherited lysosomal storage diseases caused by deficiencies in enzymes involved in glycosaminoglycan (GAG) catabolism. The resulting accumulation of GAGs in tissues and organs leads to skeletal and joint abnormalities (hip dysplasia, knee or ankle valgus, kyphosis, scoliosis, atlanto-axial instability, chest deformities, joint stiffness/hypermobility), cardiopulmonary compromise (upper/lower airway obstruction, restrictive lung disease, cardiac valve disease, left ventricular hypertrophy), neurological problems secondary to spinal cord compression, hepatosplenomegaly, and impaired vision and hearing [1]. Cognitive decline occurs in severe forms of MPS I (mainly Hurler [MPS IH], Hurler-Scheie [MPS IHS] syndrome), MPS II (Hunter syndrome), MPS III (Sanfilippo syndrome) and MPS VII (Sly syndrome) [1]. There is wide genotypic and phenotypic heterogeneity among the MPS types. All are autosomal recessive disorders, except MPS II which is X-chromosome linked and typically occurs in males [1].

Recent improvements in diagnosis, multi-disciplinary care, and treatments such as enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT) have led to increased life expectancy and a growing number of adult MPS patients. Not surprisingly, MPS adults are considering starting families or are actively pursuing having children. While case reports describing fertility and pregnancy in women with MPS are rare [2–10], even less data exists on fathers

Abbreviations: ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HSCT, hematopoietic stem cell transplantation; MPS, mucopolysaccharidosis.

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with MPS. A few case reports have shown that pregnancy and delivery can be problematic in women with MPS [2–5,8]. Small stature, obstructive and restrictive respiratory disease, cardiac issues (mostly valve disease), spinal cord compression, hepatosplenomegaly, and musculoskeletal abnormalities might interfere with normal pregnancy and delivery or exacerbate due to pregnancy [11–18]. Use of steroids (as pre-treatment with ERT to avoid infusion-associated reactions) may cause adrenal insufficiency during pregnancy [19,20]. The majority of published case reports describe pregnancy and/or delivery in women with MPS I [3,4,6,7,9,21–23]. In several of these cases, pregnancy and delivery was successful [6,7,9,10,22]. One report described the case of a woman with MPS IH who had a successful bone marrow transplantation at 14 months of age [3]. Pregnancy was terminated at 9 weeks due to concerns about the patient's health and her ability to care for the baby [3]. Another report described rapid clinical deterioration of a woman with MPS I after discontinuation of ERT during pregnancy and delivery at 29 weeks of gestation of a baby of 1.25 kg [4]. Problems achieving adequate combined spinal-epidural anesthesia and the need for emergency tracheostomy during planned cesarean section has been reported for a 23-year-old woman with MPS IHS who had received ERT for over 10 years [21]. A 37-year-old woman with MPS IS receiving ERT developed signs of pre-eclampsia with hypertension and albuminuria at the end of pregnancy and significant aggravation of preexisting valve disease after delivery [23]. Two case reports discussed pregnancy/delivery in women with MPS IVA. One of the women developed polyhydramnios and dyspnea in the 21st week of gestation and delivered a premature baby of 1.18 kg at 28 weeks [2]. The other case report concerned inadequate pain management during epidural anesthesia for cesarean section, probably due to a combination of kyphoscoliosis, lumbar canal stenosis, and thecal sac compression [8]. Only one published case report discussed pregnancy and delivery in a woman with MPS VI [5]. She developed severe myelopathy in the third trimester of pregnancy due to compression of the cervical spinal cord.

2. Methods

The case series presented here follows eight women and five men with MPS and explores the pregnancy issues associated with their disease. The cases were presented at an advisory board meeting on pregnancy and fertility in MPS patients held April 18th, 2015 in Berlin, Germany, and attended by international MPS experts.

3. Case reports

3.1. Demographics and clinical characteristics (Table 1)

Eight women and five men with MPS were followed at six tertiary care centers in the US, UK, France, Austria, and Germany. The 13 cases involved MPS IHS, MPS II, MPS IV (Morquio syndrome) A and B, and MPS VI (Maroteaux-Lamy syndrome). Each patient depicted in this publication provided written informed consent. The men with MPS II were brothers. Although most of these patients had attenuated phenotypes of MPS they all showed clear manifestations of the disease, including musculoskeletal, respiratory, cardiac, and/or neurological problems. Two patients showed severe short stature, below 125 cm (Table 1). None had psychological or intellectual regression. One of the men with MPS II (case 9) died at 28 years of age, 6 months after undergoing a lung transplantation and less than 2 years after his son was born.

3.2. MPS mothers

Mean age at pregnancy of the eight women was 29.8 (SD 6.5) years (Table 1). Six women had one child. Case 3 (MPS IVA) delivered two children during the observed time interval. Case 8 has three children, of which two were born before MPS VI was diagnosed; only her third pregnancy is reported here. Case 2 (MPS IVA) had a miscarriage and an extra-uterine pregnancy followed by right salpingectomy in the year before the pregnancy. None of the other women had previous pregnancies. None of the partners had MPS.

Fig. 1 provides details on the clinical history and pregnancy outcome of cases 5 and 8. The Appendix provides an overview of all other female cases discussed.

3.2.1. Complications during pregnancy

Complications during pregnancy included lumbar pain (case 6) and migraine (cases 2 and 6) requiring paracetamol use, gastric pain and reflux requiring treatment with omeprazole (case 2), high relative weight gain (18–24% for cases 3, 4, and 5), frequent spotting at 18 weeks (case

Table 1
Demographics and clinical characteristics of the mothers and fathers with MPS.

Case	MPS type	Number of children	Age at pregnancy/birth (males), yrs	Height, cm	Weight, kg	ERT/HSCT	
						Throughout pregnancy	During lactation
MPS mothers							
1	IHS	1	22	148	NA	ERT	–
2	IVA	1	41	142	73	ERT	–
3	IVA	2	25	147	41	–	–
			28			–	–
4	IVA	1	35	114	35	–	–
5	IVB	1	31	147	45	–	–
6	VI	1	21	149	75	ERT	–
7	VI	1	32	NA	NA	–	–
8	VI	3[a]	33	146	39	ERT	ERT
Mean (SD)			29.8 (6.5)	141.9 (12.5)	51.3 (17.9)		
MPS fathers							
						At conception	
9[b]	II	1	27	170	51	HSCT (age 17)	
10[c]	II	1	24	168	77	ERT	
11	IVA	1	30	122	NA	–	
12	IVA	1	31	155	NA	–	
13	IVA	3	41, 43, 45	150	85	–	
Mean (SD)			34.4 (8.4)	153.0 (19.3)	71.0 (17.8)		

NA: not available; M: male; F: female.
[a] Only third child (first child after diagnosis of MPS VI) is discussed.
[b] Died at age 28.
[c] Expecting a second child.