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A Case Report of Pregnancy Outcome Following Four Consecutive Complete Molar Pregnancies: Review of Genetic Basis of Recurrent Molar Pregnancies and Pillars of Management

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Abstract

Recurrent molar pregnancy is a rare condition, characterized by unclear prognosis of subsequent pregnancies. This paper discusses a 25-year-old gravida 5, diagnosed with acute idiopathic polyhydramnios following 4 consecutive complete hydatidiform moles. She delivered through caesarean section secondary to breech presentation and non-reassuring foetal status following preterm premature rupture of membranes, to a live male infant. This paper reviews the genetic basis of recurrent molar pregnancies, pillars of management and the outcome of subsequent pregnancy following recurrent molar pregnancies.

Keywords: Recurrent molar pregnancy; Genetics counselling; Preconception care

Introduction

Recurrent complete molar pregnancy is rare, estimated to occur in 1% to 2% [1,2]. It is multifactorial in origin, involving various combinations of several environmental and genetic factors. It is characterized by atypical hyperplastic trophoblast and hydropic villi. It can be complete or partial. Genetic counselling and testing is often offered to affected women who usually present with two recurrent molar pregnancies. The purpose of genetic testing is to identify changes in chromosomes, genes, or proteins in order to offer adequate counselling to affected couples.

In most developing countries within sub-Saharan Africa, genetic testing is out of reach of majority of couples affected by genetic diseases. Therefore, these couples are subjected to psychological trauma, and often relationship breakdown after several pregnancy failures. In addition, recurrent obstetric events in our context, are considered to be one of the unsolved reproductive health problems in the community due to lack of information about reproductive health related-problems. Some couples persistently try until they achieve a live birth while majority turn to herbal remedies and spirituality to reach their goal. This study highlights the role of genetic testing, describes the pillars of management and outcome of subsequent pregnancy following recurrent complete hydatidiform molar pregnancy.

Case Report

25 year-old gravida 5, referred to a tertiary hospital for further management of polyhydramnios at 33 weeks. She had her first admission at 13 weeks gestation for vaginal bleeding and she was managed conservatively after ultrasound ruled out molar pregnancy. The second admission for similar symptoms was in early October 2019. In November, 2019, she had abdominal pain and distension. There was no respiratory distress and vitals were unremarkable.

Medical history was unremarkable. However, on obstetric and gynaecological history, she had been managed for recurrent molar pregnancy in 2015, 2016, 2017, and 2018. For each molar pregnancy, she underwent dilatation and curettage and was followed up on combined oral contraception with successful normalisation of β -HCG titre. The patient could not afford the

cost of genetic testing and karyotyping required on the different occasions. In addition, she did not report any family history of molar pregnancies, diabetes or other genetic disease. However, there was a positive report of an episode of depression related to previous obstetric events.

Her laboratory investigations revealed that her blood group was O positive, and the rest of antenatal profile was unremarkable. The screening for gestational diabetes was also unremarkable. An obstetric scan done on 04/11/2019 showed a single live intrauterine pregnancy in breech presentation at 33/40 + 1/7, EFW 2060 +/- 309 g, biophysical profile of 8/8, umbilical artery resistive index of 0.57, middle cerebral artery resistive index of 0.62, and amniotic fluid index of 37.16 cm indicating polyhydramnios. The placenta was noted to be anteriorly located with a smaller placental lobe that was appreciated on its the posterior aspect. An amniotic band connecting the two lobes was noted and the placenta was succenturiate. The foetal anatomy was grossly normal and the cardiotocography (CTG) was reassuring.

On 20/11/2019, the patient complained of drainage of liquor. On speculum examination, the os was open and there was active drainage of clear, non-foul-smelling liquor. A decision to perform an emergency caesarean section was made due to breech presentation, and a non-reassuring category II CTG tracing with late decelerations and no accelerations. The emergency caesarean section was done, the outcome of which was a live male infant with a birth weight of 2400grams. The APGAR score was 6, 7, 8, at one, five and ten minutes, respectively. The baby was admitted to newborn unit secondary to respiratory distress. Placental separation failed to occur after delivery of the baby and it was therefore manually removed, and the diagnosis of placenta accreta was made. The estimated blood loss (EBL) was 600mls.

Discussion

Hydatidiform moles are abnormal conceptions, and most cases are sporadic while a small proportion of them are recurrent and often familial. Etymologically, the term hydatidiform mole comes from the Greek words hydatisia which means drop of water, whereas mola means false conception [2]. To date, the recurrent form of the disease carries different names such as recurrent hydatidiform mole, recurrent molar pregnancy and habitual complete molar pregnancy. It is defined by repeated occurrence of molar pregnancies; at least 2 consecutive or non-consecutive partial or complete molar pregnancies [1]. The current literature on recurrent molar pregnancy does not classify the disease as primary or secondary RMP. [1]. Familial recurrent hydatidiform mole is an exceedingly rare condition, in which complete hydatidiform moles are mostly diploid but biparental in origin and the outcome of subsequent pregnancies is likely to be a hydatidiform mole or other type of reproductive loss, which occurs in women of the same family (mostly first and second degree relatives) [1,2].

Current evidence has shown that the risk of a second molar pregnancy is 1% to 6% for a woman who has two molar pregnancies, the risk of having a third increases up 15_28% [3], and to nearly 100% following the three consecutive molar pregnancies. In line with this, studies have shown that the elevated risk of recurrence appears to persist even when the woman has a different male partner for the different pregnancies. The exact mechanism is not well understood; however, studies support the theory that the occurrence of three molar pregnancies is responsible for disrupting normal oocyte fertilization with no paternal genomic involvement [4]. Furthermore, in women with recurrent disease, there is up to 68 to 80% risk of having the same histological type of disease [5]. This is because of the paternal aetiology of the disease, when most of women do keep the same partner. The familial inheritance of the condition is also another explanation of having the same type and recurrent disease as well. This is important information for obstetricians and gynaecologists when providing counselling to affected women of reproductive age. After one molar pregnancy, preconception counselling should be initiated as part of preconception care. The purpose is to identify and assess risk factors [6]. The patient's previous history or family history of recurrent pregnancy loss are very important details to be noted by the clinician. During counselling, the clinician should be able to identify modifiable and non-modifiable risk factors. The modifiable risk factors of molar pregnancy include smoking, use of combined oral contraception, nutritional deficiency (deficient dietary intake of vitamin A, animal fat, and beta-carotene). Non-modifiable factors include maternal age and blood group type, previous history of molar pregnancy, family history of recurrent molar pregnancies and genetic factors. The non-modifiable factors should be carefully assessed and serve as basis for adequate counselling for risk of recurrence in subsequent pregnancy and/or pregnancy outcome. On the basis of the evidence currently available regarding subsequent pregnancy following molar pregnancy, majority of women (>98%) who conceive following a molar pregnancy will not have another hydatidiform mole and these pregnancies are at no increased risk of other obstetric complications [3]. The pillars of management of recurrent molar pregnancy include patient's history, genetic testing and counselling, psychosocial management involving a multidisciplinary team, and indulgence of the patient's desire for childbearing to keep trying provided there are no additional morbidities.

Recurrent molar pregnancy is multifactorial involving various combinations of several environmental and genetic factors. The genetic basis of hydatidiform mole was established in the 1970's. All complete molar pregnancies have a diandric paternal only genome; there is no maternal contribution [7,8]. Majority of them are therefore homozygous and arise from an anuclear empty ovum that has been fertilised by a haploid 23, X sperm (monospermy), which then replicates its own chromosomes resulting in a 46,

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XX karyotype (uniparental paternal isodisomy) [3]. In addition, a minority involve the fertilisation of an anuclear empty ovum with two sperm (dispermy) simultaneously, which can result in a 46, XX or 46, XY karyotype (uniparental paternal heterodisomy) [5]. To date, two genes have been identified to be responsible for recurrent molar pregnancies. These include NLRP7 and KHDC3L (also known as C6ORF221) [5,6], accounting for up to 80% and 5% of cases, respectively [5]. Evidence has shown that the two genes are critical for normal oocyte development, which in turn impacts the embryonic development. The NLRP7 is a nucleotide oligomerization domain (NOD)-like receptor, pyrin containing 7, maps to 19q13.4, found in several human tissues, including endometrium, placenta, hematopoietic cells, all oocytes stages, and preimplantation embryos. It is the first identified causative gene for RMP, and there are 47 mutations in NLRP7 in patients with two defective alleles [5,6]. These mutations include stop codons, small deletions or insertions (less than 20-bp), splice mutations, large deletions or insertions, and complex rearrangements. Mutations in multiple genes result in the production of proteins with impaired function, affecting the normal development of the oocytes, cause of RMP [6,9]. The NLRP7 or KHDC3L gene mutations can also prevent proper imprinting of multiple genes that contribute to a developing embryo, leading to abnormal gene activity (expression) [9]. However, it is not clear if problems with imprinting also contribute to the development of a hydatidiform mole. The NLRP7 is a member of the NLR family of proteins with a role in inflammation and apoptosis. Studies have indicated that its overexpression in transient transfections downregulates the production of IL-1β, an important mediator of the inflammatory response. Recently, 1 study showed another role of NLRP7. Its knockdown in human embryonic stem cells and leads to an earlier expression of two trophoblast differentiation markers, GCM1 and INSL4, suggesting that NLRP7 loss of function accelerates trophoblast differentiation [10,11].

Regarding the KHDC3L (KH domain containing 3-like), it is the second recessive gene responsible for RMP, identified in 2011 [7,8]. According to the evidence currently available, KHDC3L is a minor gene for RMP, accounting for10–14% of patients who do not have mutations in NLRP7. Similar to NLRP7, the KHDC3L transcripts have been identified in several human tissues, including all oocytes stages, preimplantation embryos, and hematopoietic cells.

To date, it is recommended that NLRP7-DNA testing should be offered to all women with at least two RMP. Methods currently in use rely on PCR amplification of the 11 exons of NLRP7 from genomic DNA. In addition, patients without NLRP7 mutations should be screened for KHDC3L mutations [7]. Authors of the current report acknowledge the evidence, which encourage genetic testing and karyotyping, as an important component of the management of affected women. The challenge of getting both genetic testing and karyotyping in resource-limited settings of sub-Saharan Africa is recognized as limitation, which handicaps the preconception counselling.

With regard to obstetric outcome following recurrent complete molar pregnancies, available evidence shows that it is possible to have normal pregnancy and achieve live birth even after 4 consecutive recurrent molar pregnancies. In relation to this finding, different studies from various groups of population have shown that the chances of achieving a live birth are as low as 3% in women with two defective alleles in NLRP7 [9]. In addition, few studies have reported about 10-20% increased risk of pregnancy losses following recurrent molar pregnancies. This is 2-4 times higher compared to the general population [8,9]. However, the case report has never had normal pregnancy; in contrast, her obstetrical history was characterized by habitual molar pregnancies and depression. However, the presence of polyhydramnios was interpreted as major abnormal finding which needed further investigation to determine the cause. Polyhydramnios is caused by increased secretion of amniotic fluid because of large placenta observed in pregnant women with diabetes, syphilis, or multiples gestation. Immune and non-immune foetal hydrops; or by foetal malformation that prevents the foetus swallowing fluid (anencephaly, oesophageal atresia) or absorbing fluid through the intestinal villi [9]. None of these conditions was found, and the diagnosis of idiopathic acute polyhydramnios was made. To date, there is limited data regarding the development of acute or chronic polyhydramnios following sporadic or recurrent molar pregnancy. Otherwise, it is possible to develop idiopathic polyhydramnios which currently accounts for up to 60% of polyhydramnios cases. However, there is no evidence of increased risk of polyhydramnios following recurrent molar pregnancies. Therefore, although successful pregnancy rate is very low in women with recurrent molar pregnancy, the management approach of their childbearing desire should indulge their wish to keep trying. It is important to empathize with them regarding their desire and manage the psychosocial aspect of pregnancy loss using a multidisciplinary approach.

Conclusion

Recurrent complete molar pregnancy is multifactorial. Two genes, NLRP7 and KHDC3L are responsible for recurrent disease. Therefore, all women with at least two recurrent molar pregnancies should be offered genetic testing. Those with two defective alleles in NLRP7 should receive appropriate genetic counselling about the poor prognosis of subsequent pregnancies, including risk of choriocarcinoma.

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Ethics Approval

A formal approval from Moi University-Moi Teaching and Referral Hospital Institutional Research and Ethics Committee (IREC).

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