

# Sextuplets: management of a higher order pregnancy in a medium-resource setting

## Abstract

A 28-year-old gravida 1 para 0 was referred to the Mt. Hope Maternity Hospital, a tertiary teaching institution at 8 weeks of gestation with excessive vomiting in pregnancy secondary to a sextuplet pregnancy. She was given empirical clomiphene citrate 100mg for 10 days after having difficulty conceiving with known polycystic ovarian syndrome. She conceived after the first course of clomiphene citrate. After being counseled on the many maternal and fetal complications with higher-order pregnancy and a clear road-map for the management of the pregnancy, which included multifetal pregnancy reduction (MFPR), this was declined due to socio-cultural and ethical grounds.

Cervical cerclage was inserted at 12 weeks gestation and thromboprophylaxis commenced. Urgent Caesarean delivery was arranged at 31 weeks of pregnancy secondary to worsening symptoms of overdistension. This study aims to outline management of a higher order pregnancy when the standard approach of MFPR is unacceptable to the patient. Central to this cause was circumventing risks of higher order gestations such as preterm labor, pre-eclampsia, thrombosis and anaemia.

**Keywords:** Fertility and assisted reproduction, General obstetrics, Maternal medicine, Fetal medicine, Multiple gestation, Clomiphene citrate

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**Abbreviations:** MFPR, multifetal pregnancy reduction; PCOS, polycystic ovarian syndrome; PAHO, Pan-American health organization; OI, ovulation induction; SO, superovulation; ART, assisted reproductive technologies

## Introduction

From 1968 to present only seventeen accounts of sextuplet births have been published. The most recent of these cases being the aforementioned case managed at Mt Hope Maternity Hospital, Trinidad and Tobago. The question of 'best practice' management of higher-order pregnancy (3 or more fetuses) is still relatively new and controversial with the incidence of the pregnancies skyrocketing in the 1960's as drugs for the treatment of infertility became commercially available. It is estimated that approximately 20% of higher order births are naturally conceived while the remainder are related to ovulation induction/superoovulation and assisted reproductive technologies (ART). Higher order pregnancies by all means should be considered a very high-risk pregnancy as it carries a significant chance of fetal and maternal morbidity. The surveillance of these complications must be thoughtfully carried out and tailored to include risk factors and complications of multiple gestations.

## Clinical case

Ms. PLF, a 28-year-old gravida 1 para 0 was referred to the Mt. Hope Maternity Hospital, a tertiary teaching institution at 8 weeks of gestation with excessive vomiting in pregnancy secondary to a sextuplet pregnancy. She denied experiencing abdominal pain, vaginal bleeding, urinary or any other gastrointestinal complaints. A transabdominal ultrasound confirmed the six fetuses were alive. She remained in hospital for five days for rehydration and parenteral anti-emetic agents. With the involvement of her partner and the obstetric and neonatal teams, she was counseled on the many maternal and fetal complications with higher-order pregnancy and a clear road-map for the management of the pregnancy, which included multifetal

pregnancy reduction (MFPR) was declined due to socio-cultural and ethical grounds.

She had a history of irregular menstrual cycles secondary to polycystic ovary syndrome (PCOS) for which a low-dose oral contraceptive pill was prescribed. After discontinuation of the pill she was unable to conceive despite regular unprotected coitus for six months. She was then given empirical clomiphene citrate 100 mg for 10 days. She conceived after the first course of clomiphene citrate. There was no other significant medical nor surgical history.

At 12 weeks of gestation, a repeat ultrasound scan done for chorionicity revealed that the fetuses were in separate sacs. The cervix was found to be effacing with a length of 2.0 cm. A cervical cerclage using mersilene tape and with the McDonald's method was performed under general anaesthesia. Micronised progesterone vaginal tablets 100 mg daily were started and this was increased to 200 mg at 20 weeks gestation. She was also admitted to the hospital for bed rest as she was experiencing uterine contractions. Salbutamol was also commenced as a second tocolytic agent.

She remained normotensive, and an oral glucose tolerance test was normal. Calcium was given as prophylaxis against pre-eclampsia and therapeutic iron was administered. Thrombo-embolic stockings and low-molecular weight, enoxaparin were recommended. An anatomy scan excluded gross structural abnormalities. The placenta was low-lying. Fortnightly growth scans revealed normal biometric measurements. Frequent mid-stream urine samples and high vaginal swabs were negative.

At 25 weeks the haemoglobin level dropped to 7.0 g/dL, and two units of packed cells were transfused. One week later, four doses of dexamethasone were given intramuscularly for promotion of fetal lung maturity.

A meeting with the multidisciplinary team was reconvened as we had gone beyond the age of viability. The decision derived included

delivery via an elective caesarean section at 32 weeks. She was counseled that there was a risk of uncontrollable intra-operative bleeding which may require an emergency hysterectomy. The involvement of the Ministry of Health, other governmental agencies, Pan American Health Organization (PAHO), other senior members of the regional health authority was obtained especially to provide the hospital with adequate ventilators and other hardware. The assistance of the Heads of the other two neonatal units in the country was also requested.

She did well until 31 weeks when she experienced severe difficulty in breathing, with a drop in oxygen saturation to 90%. The cardiologist and respiratory physician agreed that the cause was likely to be due to uterine overdistension and they recommended imminent delivery.

The next day, under general anaesthesia and the participation of three senior obstetricians, a lower segment caesarean section was performed. The babies were delivered by breech extraction through an anterior placenta praevia type 3. A combination of oxytocin, syntometrine, carbetocin and misoprostol was given. The placenta was delivered with the Brandt-Andrews method. The uterus was exteriorized and massaged. The cavity was swabbed and no active bleeding was seen in the lower segment which was closed in two layers with vicryl. Bilateral tubal ligation was done and the abdomen closed in the usual manner. At the end of the procedure the cerclage was removed and the vagina was swabbed. The estimated blood loss was 2000ml.

Each baby upon delivery was received by a separate midwife who took the baby to a pre-assigned resuscitation station manned by a team headed by a neonatologist and included two registrars. Subsequently, the babies were transferred to the neonatal intensive care unit. There, another team of doctors continued the management. The birth weights varied from 800 to 1300g. Apgar scores were greater than 6 at one minute. Respiratory support varied from intermittent positive pressure ventilation to oxygen via head box.

The patient received two units of blood while in the recovery room. Her vital signs remained normal. She made an uneventful recovery and she was discharged on day-6 post-surgery. She received social and financial support from the government. One of the babies died after 28 days from a congenital chest abnormality and two others succumbed later from sepsis. The other three babies have been developing normally.

## Discussion

The goal of infertility treatment is for each patient to have one healthy child at a time. Regardless of which infertility treatment from ovulation induction (OI) with clomiphene citrate, gonadotrophin releasing hormone or aromatase inhibitor, letrozole to superovulation (SO) and assisted reproductive technologies (ART), the objective is the same: to maximize the probability of a successful pregnancy while minimising the risk of a multiple gestation especially higher-order multiples.<sup>1</sup> From 1968, 17 reports of sextuplet births have been documented with the last by Warraich and Vause<sup>2</sup> who reported on the first possible set of sextuplets conceived with letrozole, but this pregnancy ended as a spontaneous miscarriage at 19 weeks. Our patient appears to be the last sextuplet to achieve viability following Clomiphene therapy since 2013.

Despite the recommended dose schedule, to initiate Clomiphene treatment with 50mg daily on cycle days 2 to 5, for 5 consecutive days with sequential increases of 50mg in subsequent cycles if anovulation persists,<sup>3</sup> this patient received a high initial dose which may have led to this sextuplet.

Clomiphene citrate, a selective oestrogen-receptor modulator that antagonises the negative feedback of oestrogen at the hypothalamus with a consequent surge in the release of gonadotrophins from the anterior pituitary, has been used for decades and is the recommended first-line therapy. It is inexpensive, well-tolerated, safe, and the risk of ovarian hyperstimulation syndrome is 2 of 1095 patients.<sup>4</sup>

That multiple gestations and especially higher-order multiples are associated with increased maternal morbidity, and fetal and neonatal morbidity and mortality have been established by several studies.<sup>5,6</sup> The most likely complications are pre-eclampsia, preterm labour, and very low birth weights, and gestational diabetes mellitus. Prematurity accounts for the poorer perinatal outcome as the number of fetuses increases. This patient was referred to us due to the expected high risks associated with this higher-order pregnancy.

In order to reduce the risk of pre-eclampsia, prophylactic calcium supplementation was administered.<sup>7</sup> Gestational diabetes mellitus was ruled out with a formal 75g oral glucose tolerance test. These medical disorders of pregnancy are further increased as she had a history of PCOS. As she was hospitalised for a prolonged period of time thrombo-embolic stockings and low-molecular weight heparin, enoxaparin were advised. She developed anaemia due to an exaggerated haemodilutional effect from a marked rise in plasma volume as compared to that of red cell mass. A top-up transfusion was performed to achieve a satisfactory haemoglobin. This was necessary due to the presence of placenta praevia, a condition linked to excessive blood loss at the time of caesarean section sometimes requiring an emergency hysterectomy.

The major challenge was to prolong this pregnancy with the aim of reducing the risks of extreme prematurity. Cervical assessment at the end of the first trimester revealed the presence of effacement of the cervix for which a cervical cerclage was inserted. Despite extensive counseling on the possible benefits of multifetal pregnancy reduction (MFPR) to a twin gestation, she declined the offer. The literature on the possible benefits of MFPR is depleted due to a lack of randomised trials assessing efficacy and a paucity of meta-analyses.<sup>8</sup>

We employed various pharmacological approaches to mitigate against early preterm delivery initially with progesterone vaginal tablets once daily, and then twice daily, and at 20 weeks salbutamol was added as she experienced contractions. She was counselled on the risk of pulmonary oedema with beta-agonists and also the limited documented efficacy of tocolysis especially in prolonging a pregnancy for more than seven days. Micronised progesterone which allows for either oral or vaginal administration was chosen since it affords enhanced bioavailability, and less side effects such as sleepiness, fatigue and headaches compared to intramuscular 17-hydroxy progesterone caproate.<sup>9</sup> NICE guidelines<sup>10</sup> endorse the use of progesterone and cervical cerclage in women also with a short cervix and a history of preterm births among singleton pregnancies.

That we fell short of the target time of delivery at 32 weeks emphasises the need for detailed advanced preparation with the likelihood of early delivery of very premature babies. She was delivered at 31 weeks due to severe maternal respiratory embarrassment from splinting of the diaphragm due to the marked overdistension of her uterus. It is evident that the literature has a paucity of information in the planning and logistics of effecting the delivery of higher-order pregnancies. The NICE quality standard<sup>11</sup> recommended a multidisciplinary core team to manage twins and triplet pregnancies, and that a discussion by 24 weeks with the patient on clinical features of preterm labour and possible adverse perinatal outcomes. We engaged several agencies including PAHO, Ministry

of Health and other governmental agencies for provision of adequate hardware such as ventilators and nursery cots. The Heads of the other two neonatal units in the country were involved as well in case some babies had to be transferred to their institutions.

Our core team for delivery included three senior obstetricians, two consultant anaesthetists, six midwives (one for each baby), and six adjacent stations, each manned by a team of a neonatologist and two registrars. A brief rehearsal was conducted prior to the delivery for the transport and care of the babies in the operating theatre. This allowed a seamless transfer of each baby upon delivery to his predetermined station and then the neonatal unit.

We endorse the views of others that more clinical research to identify methods of delaying preterm births among higher-order pregnancies is necessary.<sup>12</sup> Furthermore, the increased complication rates associated with multiple pregnancies should be taken into account when women are being counseled on infertility treatment.

The need for thorough planning of the delivery and immediate care of the newborns with multiple pregnancies to achieve a good outcome is essential. Higher-order pregnancies lead to tremendous strain on limited health services and social and economic resources of the country, in addition to the great stress for the concerned family and every effort should be put in place to minimise these pregnancies.

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## Conflicts of interest

None of the authors have any conflict of interest with regard to this article.

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