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## Quadruplet pregnancy after ovarian stimulation: the role of the counseling program to avoid dangerous pregnancies

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### ABSTRACT

The incidence of high-order multiple gestation (HOM) (triplet and quadruplet pregnancies) has increased noticeably in the last few years due to the increase of medically assisted reproduction techniques. In order to reduce these generally unsafe pregnancies, different solutions are available such as embryo reduction. However, the best and most ethical method is prevention. It is strongly suggested to assign these procedures to a fertility specialist with experience in preconception counseling in order to establish a good relationship between the physician and the couple. When HOM occurs, identifying the optimal gestational age for delivery becomes a mandatory goal for its management. We describe a case of a woman with a history of infertility who had ovarian hyper stimulation and, as a consequence of an inadequate medical compliance, a quadruplet pregnancy.

**Key words:** high-order multiple gestation, cesarean section, ovarian hyperstimulation, quadruplet gestations.

### SOMMARIO

Il numero di gravidanze multiple con un numero di feti superiore a due (HOM) è aumentato sensibilmente negli ultimi anni a causa dell'incrementato uso di tecniche di riproduzione medicalmente assistita. Al fine di ridurre queste gravidanze potenzialmente pericolose, diverse soluzioni possono essere valutate, tra le quali la discutibile embrio riduzione. Tuttavia la prevenzione rappresenta la scelta più etica e sicura. Al fine porre la donna a un simile rischio, è molto consigliabile assegnare queste procedure a uno specialista con esperienza nel campo dell'infertilità e che, durante il counseling preconcezionale, sia capace di instaurare una fiduciosa collaborazione tra il medico e la coppia. Quando tuttavia la HOM si verifica, individuare l'età gestazionale ottimale per il parto diventa un obiettivo essenziale. Qui di seguito riportiamo il caso clinico di donna con storia d'infertilità che a seguito di un'inappropriata gestione e counseling preconcezionale è andata incontro a una gravidanza quadrigemina insorta su un quadro d'iperstimolazione ovarica.

### INTRODUCTION

The incidence of high-order multiple gestation (HOM) has increased drastically in the last few years. Spontaneous twin pregnancy occurs with a frequency of 1:90. According to Hellen's rule, it is possible to estimate that quadrigeminal

gestation occurs with a frequency of 1:833<sup>(1,2)</sup>. Between 1980 and 2009 epidemiological reports showed an increase in multifetal pregnancies of 76% for twin pregnancies and 400% for more than two pregnancies<sup>(3)</sup>. HOM is correlated with several maternal and fetal negative outcomes. Firstly, triplet and quadruplet pregnancies are affected by a higher perinatal mortality because of an unavoidable higher rate of pre-term delivery (mean gestational age of 31 + 5 and 29 + 5 weeks,

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respectively) and intra uterine growth restriction<sup>(4,5)</sup>. The intrauterine death rate increase for HOM from 1% in singleton pregnancies to 5%, and neonatal morbidity, neonatal and perinatal mortality is significantly higher in quadruplets compared to triplets and twins<sup>(6)</sup>. Respiratory distress syndrome has a rate of 23% for triplet pregnancies and 65% for quadruplet pregnancies. Other adverse outcomes such as intracranial hemorrhage, retinopathy of prematurity and feto-fetal transfusion syndrome (FFTS) are correlated with the number of fetuses and occur more frequently in a quadruplet pregnancy<sup>(7,8)</sup>. The most common maternal adverse events are: preeclampsia 32%, anemia 25%, postpartum hemorrhage 21% with a higher risk of emergency cesarean hysterectomy<sup>(8-10)</sup>. Several measures could be adopted to reduce these unsafe pregnancies: for example the use of specific markers for early prediction of high-risk pregnancy such as preeclampsia is reasonable<sup>(11)</sup> or in "extrema ratio" embryo reduction. Periti et al. have shown that embryo reduction performed in trichorionic triplet pregnancies does not influence the rate of miscarriages, whereas the rate of pre-term delivery (before 32 weeks) is higher in women managed expectantly<sup>(12)</sup>. Embryo reduction (ER) is undertaken with the aim of reducing maternal morbidity and mortality and improving fetal outcome but is not appropriate for all multiple pregnancies, and also it is forbidden in several countries causing many ethical controversies<sup>(13)</sup>. Certainly, the best ethical modality to avoid an HOM secondary to medical treatment is prevention. Fertility preservation is a crucial aspect of the psychological, social and physical wellness of a woman and this aspect must be considered in all gynecological disorders<sup>(14-21)</sup>. However, especially in an infertile couple and/or in a nulliparous women, fertility preservation and reproductive care must be absolutely warranted by the presence of a fertility specialist team that work in an approved reproduction center, with good experience in preconception counseling and are capable of reaching a straightforward collaboration and a complete compliance with medical advices<sup>(22)</sup>. In fact, the Health Council of Italy has defined the role of psychological support and counseling for couples with infertility problems. In specific guidelines published in 2008, the necessity to offer psychological support to all couples from the early stages of the diagnostic and therapeutic process of infertility has become obligatory<sup>(23)</sup>. Herein we report a case of a spontaneous HOM as a consequence of

incomplete preconception counseling performed in an unapproved reproduction center.

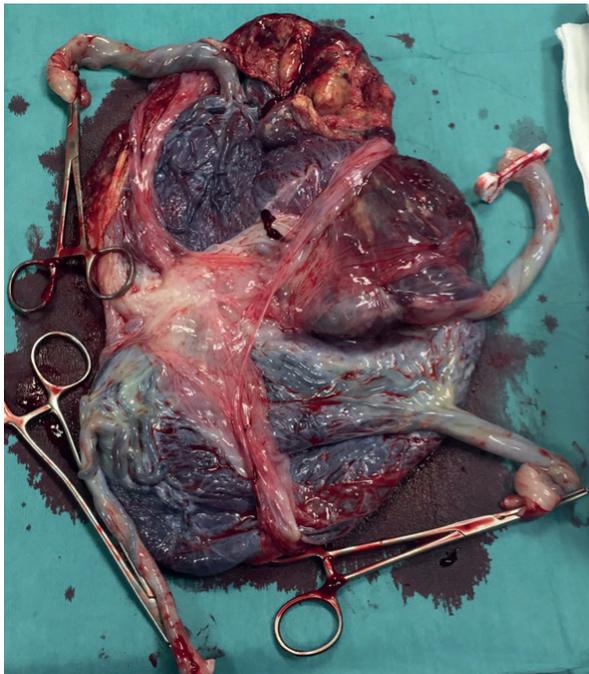
We also discuss our clinical management of this quadruplet pregnancy from a hyper stimulation syndrome.

## CASE REPORT

A 31-year-old Caucasian woman, parity 0030. was referred to our department secondary to an ovarian hyper stimulation syndrome (OHSS) where, successively, there was a spontaneous quadruplet pregnancy. As standard protocol of the university hospital in which the case was reported, the patient was informed and signed a consent allowing data collection for research purposes.

This case report is in accordance with the Helsinki Declaration, conforms to the Consensus-based Clinical Case Reporting Guideline Development (<http://www.equator-network.org/>) the Committee on Publication Ethics (COPE) guidelines (<http://publicationethics.org/>) and was approved by the Institutional Review Board (IRB) of the university hospital in which it was carried out. Her medical history was remarkable for the presence of heterozygous mutation of methylenetetrahydrofolate reductase (MTHFR), polycystic ovarian syndrome (PCOS), obesity (BMI: 34) and recurrent abortions. She was referred to an external reproduction center to have a first line ovarian stimulation and underwent 3 cycles of clomiphene citrate and menotrophin without a positive response. After the last cycle, the patient developed OHSS. She was not well informed about her situation and the fertility specialist team probably underestimated the social-cultural limits of the couple in understanding the risk of a potential pregnancy arising from this clinical condition. Despite the interruption of stimulation and the medical advice, they voluntarily decided to ignore it and had unprotected sexual intercourse. After 6 weeks she was referred to our department for moderate OHSS (ovarian size > 8 cm, <12 cm, moderate abdominal pain, and ascites)<sup>(24,25)</sup> and hospitalization was required. During the early standard evaluations a vital quadruplet monochorionic monoamniotic pregnancy was diagnosed. The fluid balance, the amount of abdominal ascites and the hematocrit level was monitored daily. Low molecular weight heparin (LMWH) for thrombosis prophylaxis was administered for the entire hospitalization period. Hospital discharge was 10 days later because of spontaneous OHSS regression.

After hospital discharge she was periodically evaluated to check pregnancy status. Periodical physical examinations, vital sign collection, ultrasound scan (US) (including biometric measurement, placental evaluation, amniotic fluid index, Doppler velocimetry of the umbilical artery and the middle cerebral artery), and gestational diabetes screening, were performed according to the international guidelines for twin prenatal care<sup>(26)</sup>. Prophylaxis for infant respiratory distress syndrome (IRDS) was made at 24 weeks. At the 26th week, after a negative screening for gestational diabetes mellitus, she was admitted to hospital again because of the IUGR of one fetus and altered Doppler velocimetry: Pulsatility Index (PI) UA 1.55; PI MCA 1.95. We decided to perform a careful wait-and-see management with periodical (every 6 days) full US evaluation until the 30th week, when worsening velocimetry values of the IUGR fetus (PI UA 1.93; PI MCA 1.09) were seen. A single dose of betamethasone 12 mg was administered and 12 h later a cesarean section (CS) was performed. Four vital fetuses were born (I, III, IV fetuses in cephalic presentation, II fetus in breech presentation): two male and two female monochorionic monoamniotic twins (**Figure 1**), weighing 1,560 gr, 1040 gr, 930 gr and 1300 gr, respectively. The Apgar score at 5 min was 7/10, 8/10, 7/10 and 9/10, respectively. All babies had respiratory distress syndrome (RDS) treated with intubation surfactant extubation (INSURE).



**Figure 1.**  
Postpartum chorionic evaluation.

One baby had an intra-ventricular hemorrhage (IVH) and the smaller female also had grade III premature retinopathy (ROP) treated with laser-therapy. The patient had no complications and was discharged from hospital after 5 days. All babies were discharged separately from the intensive neonatal care unit from 4 to 28 days after birth.

## DISCUSSION

Despite the rarity of spontaneous trigeminal and quadrigeminal gestations, these overall rates of HOM have increased due to the escalation of medically assisted procreation (MAP) techniques, which account for more than 90%<sup>(27)</sup>. Clomiphene citrate, usually associated with other drugs and nutraceutical agents<sup>(28-35)</sup>, is one of the most common first line treatment in women with anovulatory infertility (AI)<sup>(36)</sup>. Ever more women undergo medical treatment for AI due to polycystic ovarian syndrome (PCOS), the main cause of AI, which affects 4%-8% of women in reproductive age and is not always properly diagnosed and treated<sup>(37-41)</sup>. Moreover, in our case, the administration of clomiphene was not completed properly. It has been shown that the use of metformin in association with clomiphene or letrozolo is associated with a lower risk of multiple pregnancies, especially in women with metabolic dysfunctions<sup>(41-44)</sup>. The risk of an HOM as a consequence of medical stimulation is notable and physicians have to consider these metabolic alterations to prevent adverse effects including OHSS<sup>(45,46)</sup>. When OHSS occurs, pregnancy should be avoided because the rising level of human chorionic gonadotrophin (hCG) can worsen the syndrome<sup>(47)</sup>. As highlighted in our case, counseling and patient compliance are important factors that should not be underestimated, particularly when complex therapies are commenced.

Nevertheless, pregnancy can begin from an OHS scenario. When it happens, the main efforts required are: treat OHSS until complete regression (therapeutic abortion is contemplated); considering the pregnancy as a high-risk pregnancy and consequentially properly checked using standard guidelines; define the best time and modality for delivery<sup>(24,48)</sup>. According to these notions, we admitted the woman to our department for a short preliminary hospitalization to monitor the mother's condition in order to

avoid an escalation to severe OHSS. Successively, when a safe maternal-fetal condition was assured, the identification of the optimal gestational age for delivery, considering the balance between preterm complications and intrauterine adverse conditions, was the main target for the correct management of an HOM. The significant perinatal mortality is caused by the high incidence of small for gestational age (SGA), low birth weight and intrauterine growth restriction (IUGR), which correlates with prematurity and occurs in 40% of two-multifetal gestations and in approximately 100% of higher than two-multifetal gestations. Long-term consequences and disability, especially cerebral palsy, are more common among newborns of multiple pregnancies<sup>(49,50)</sup>. Intrauterine death of one twin has an incidence of 0.5% - 6.8%, although an exact estimation of intrauterine death in quadrigeminal pregnancy cannot be deduced from the current literature. Furthermore, monochorionic twin pregnancy doubles the probability of intrauterine death and increases the probability of contemporary cerebral palsy in the surviving twin. In addition, disseminated intravascular coagulation (DIC) has a higher incidence in multifetal pregnancy when compared to normal pregnancy<sup>(51)</sup>.

A retrospective study based on 100 women with multifetal gestation pregnancy showed that the average gestational age for delivery in quadrigeminal pregnancy was 29 weeks and 5 days

and the perinatal mortality, hyaline membrane disease (RDS) and intracranial hemorrhage were, respectively, 36%, 65% and 15%<sup>(7)</sup>. The same authors also showed a significant high rate in morbidity, despite the relative low rate in mortality; furthermore, they underlined that reaching a gestational age  $\geq 30$  weeks appears to be a protective factor, capable of lowering the neonatal complication rate. Considering this literature evidence and the worsening flowmetry values of the smaller fetus, we decided to perform a CS at the 30th week. Despite the fact that CS is not mandatory for HOM, no robust data have been gathered for neonatal outcomes and mortality in quadruple pregnancies, especially when concomitant IUGR of one or more fetuses occurs.

## DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. No specific funding was obtained.

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