

# Fetal Reduction in High Order Pregnancy; A Retrospective Observational Study

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## Abstract

**Background:** High order multiple pregnancies (HOMP), is considered a high-risk gestation because it is associated with multiple complications on the mother and the fetuses, with a huge financial burden on the hospitals. Avoiding HOMP for the mother is important, however, if this fails, a fetal reduction is an acceptable alternative procedure to reduce maternal complications and improve fetal outcome.

The objective of this study was to evaluate the impact of a fetal reduction on the risk of preterm labour and postpartum hemorrhage in HOMP (More than Triplet).

**Methods:** This was a retrospective study of all HOMPs seen during the period from July 2007 to July 2017 at Women's Hospital- Hamad General Hospital, Doha, Qatar. We examined records of 50 women diagnosed with HOMP. Incomplete records and triplet pregnancies were excluded from the study. The data were collected from the ultrasound software as well as maternal files.

**Results:** Of the 50 women diagnosed with HOMP, 39 quadruplets, 7 quintuplets, 2 sextuplets, and 2 septuplets. 56% had an ovulation induction, 26% had an IVF, 14% had an IUI, and 2 cases 4% were spontaneous pregnancies.

28% had a fetal reduction with a mean gestation age of  $12.64 \pm 0.74$  weeks of gestation and with no immediate complications.

Our study showed that there is no significant difference at the time of delivery between the reduced and non-reduced group mean gestational age at the time of delivery. For the reduced group was  $30.26 \pm 4.38$ , and  $29.39 \pm 4.78$  weeks for the non-reduced group. P-value of 0.565, 95% CI (-2.159-3.90). 44.9% had postpartum haemorrhage with a mean estimated blood loss of  $1659.1 \pm 958.5$  ml. Our study showed that there is a significant decrease in estimated blood loss in the reduced group compared with the non-reduced group with a p-value of 0.047

**Conclusion:** High-order multiple pregnancies are a result of

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modern infertility treatments and have significant serious adverse effects on the mother and the babies. Although fetal reduction reduced the rate of PPH but did not significantly improve the rate of preterm labour, hence prevention of HOMP is the primary goal.

**Keywords:** Fetal reduction, High order multiple pregnancies, Quadruplets.

## Abbreviations

HOMP = High order multiple pregnancy; IVF = In vitro fertilization; IUI = Intrauterine insemination; PPH = Postpartum haemorrhage; CI = Confidence interval; ART = assisted reproductive techniques; LSCS = Lower segment caesarean section; ND = Normal delivery; SD = Standard deviation; IUFD = Intrauterine fetal death; TTTS = Twin to twin transfusion syndrome.

## Introduction

Higher-order (triplet or more) multiple pregnancies occur when more than two fetuses are present in the uterus at the same time [1,2].

High order multiple pregnancies (HOMP) are uncommon, the reported incidence range from 0.01% to 0.07% of all pregnancies [1-3].

Spontaneous quadruplet pregnancy is rare with an incidence rate of 1 in 512000 to 1 in 677, 000 births [2].

The incidence of multiple pregnancies has increased dramatically in the last 25 years [4,5].

In United States, it is documented that HOMP has increased fourfold during the 1980s and 1990s, due to infertility treatments like Assisted Reproductive Techniques (ART) and ovulation-inducing treatments [6-8].

HOMP is considered a high-risk pregnancy as it has many complications for the mother and the fetuses with marked psychosocial and economic implications.

Prenatal morbidities as prematurity (more than 90% deliver prematurely), intrauterine growth restriction, low-birth weights, and congenital malformation have been shown to be more common in HOMP. Long-term consequences for these fetuses such as cerebral palsy and learning disabilities have been demonstrated [2,7,8].

Complications of prematurity as intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy, necrotizing enterocolitis, retinopathy of prematurity, and respiratory distress syndrome which can result in permanent injuries, including cerebral palsy, intellectual delay, chronic lung disease, and loss of vision and hearing [5].

Maternal mortality associated with multiple births is 2.5 times of singleton births [9].

Maternal morbidities such as pre-eclampsia, anaemia, postpartum haemorrhage (PPH) are higher in HOMP and up to three to seven times more common than singleton pregnancies, and these complications are usually associated with consequently prolonged hospitalization [8].

These pregnancies constitute a huge financial burden for the hospitals. Data shows that the average cost per multiple gestation delivery is greater than the average cost of in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles [8].

A study by Chambers et al. showed that the mean hospital costs of a singleton, twin, and HOMP child to age 5 years were \$2730, \$8993, and \$24 411 (in 2009-2010 US dollars), respectively, with cost differences concentrated in the neonatal period and during the first year of life. Almost 15% of inpatient costs for multiple births could have been avoided if assisted reproductive technologies (ART) twins and HOMP had been born as singletons [10].

Avoiding HOMP is important, therefore changes in ART practices, such as reducing the number of embryos transferred in ART procedures, using lower doses of ovulation induction medications or if multiple mature follicles are seen during ovulation induction the cycle will be cancelled, all these modifications have been associated with the decline in higher-order multiple births, but if primary prevention of HOMP failed, the fetal reduction is an ethically acceptable procedure and is an appropriate alternative to decrease the perinatal morbidity and mortality and to increase survival and well-being of high order pregnancy [8,11,12].

The outcome of HOMP was determined by the gestational age at delivery, the mean gestational age at delivery for quadruplet pregnancies was reported to be 31.4 weeks [5].

It is stated that the average gestational age at delivery for twins is 35 weeks, triplets 32.2 weeks quadruplets 29.9 weeks, and quintuplets 28.5 weeks [2].

Prevention and management of HOMP, therefore, poses a great challenge to the obstetrician as there is no clear evidence-based approach to its management and prevention. Bed rest, beta mimetic drugs, progestogens, and elective cervical cerclage have all been reported to have a beneficial effect in prolonging pregnancy in some literature, but the results are yet to be substantiated by controlled trials [2].

There are limited studies are reviewing obstetric outcomes following fetal reduction.

Our aim retrospectively was to review the outcomes of fetal reduction in HOMP in reducing the risk of postpartum haemorrhage (PPH) and preterm labour in quadruplets and quantuplets pregnancies.

## Materials and Methods

### Study design and study area

This retrospective study was conducted in Obstetrics and Gynaecology Department, Women's Hospital, currently known as Women's Wellness and Research Center, Hamad Medical Corporation, Doha, Qatar. Women's Wellness and Research Center is a governmental hospital and the largest women's tertiary hospital in the country with average deliveries of 17,000 births per year with 7 operating theatres and 26 delivery rooms.

## Study sample

The study sample included all medical records of 50 women diagnosed with HOMP (defined as more than triplets) who had antenatal care and gave birth in the hospital in the period from July 2007-July 2017, however incomplete records and triplets pregnancy were excluded from the study.

The data were collected from the ultrasound software (*Astraia Software GmbH Occamstr. 20, 80802 Munich Germany*) and maternal records for pregnancy progress, fetal complications, and maternal comorbidities, and delivery outcome.

The Data was kept in a password-protected Excel sheet (© 2010 Microsoft Corporation).

## Data extraction

The records included information on subjects' demographics including age, chorionicity, mode of conception, parity, maternal diseases, if the fetal reduction was done, and at which gestation? time of delivery, mode of delivery, the indication of delivery, and estimated blood loss during delivery

## Statistical analysis

Descriptive analysis of mean  $\pm$  standard deviation (SD), median, minimum and maximum for continuous variables was performed using SPSS version 20.0

Comparisons were done using T-test, ANOVA, and chi-square test.

95% CI was used to assess the statistical significance of association among variables, with a P value less than 0.05 was used as a cut-off point to see the presence of a statistically significant association.

## Ethical considerations

Ethical clearance for the study was obtained from the Medical Research Center, (MRC), Hamad Medical Corporation (HMC), Doha- Qatar, Ref No: MRC0419/2017. To protect patient confidentiality, identifiable information as the name of the patients and health number was excluded from the extracted data and replaced with a specific code generated for the study.

## Results

During the study period a total of 50 pregnant women were diagnosed with HOMP and gave birth in Women's Hospital, of these women 39 (78%) had quadruplets pregnancy, 7 (14%) had quintuplets, 2 (4%) had sextuplets, and 2 (4%) had septuplets pregnancy, with more than 95% of them conceived through ART. The mean maternal age was 30 years. 13 (26%) were nulliparous and 37 (74%) were multiparous, with no family history of multiple pregnancies before in 96% of them (Table 1).

## Time of delivery in HOMP

We had 28 women who delivered quadruplets, the mean gestational age at the time of delivery for quadruplets was 30.38  $\pm$  2.66 weeks with 95% CI (29.35-31.42). Three

women delivered quintuplets, mean gestational age at the time of delivery for quintuplets was 31.67 weeks gestation with 95% CI (25.42-37-92), using ANOVA, there is no statistically significant difference at the time of delivery between quadruplets and quintuplets (ANOVA F= 1.09, P-value = 0.346)

## Fetal reduction and timing of delivery

14 women had fetal reduction while 31 women did not have fetal reduction. The mean gestational age of fetal reduction was 12 weeks (Table 2), with no immediate postoperative complications.

The mean gestational age at the time of delivery for the

Characteristics	Mean $\pm$ SD N (%)	Median (min-max)
<b>Age</b>	30.60 $\pm$ 4.87	30.25 (19.40-39.30)
<b>Chronicity</b>		
Quadruplets	39 (78%)	
Quintuplet	7 (14%)	
Sextuplets	2 (4%)	
Septuplets	2 (4%)	
<b>Mode of conception</b>		
Ovulation induction	28 (56%)	
IVF	13 (26%)	
IUI	7 (14%)	
Spontaneous	2 (4%)	
<b>Parity</b>		
Nulliparus	13 (26%)	
Multiparus	37 (74%)	
<b>Previous miscarriages</b>		
No	33 (66%)	
Yes	17 (34%)	
<b>Previous Multiple pregnancies</b>		
No	41(83.7)	
Yes	8 (16.3)	
<b>Family Hx of multiple pregnancies</b>		
No	48 (96%)	
Yes	2 (4%)	

Table 1: The obstetric profile of women with HOMP.

<b>Fetal reduction</b>		
No	31 (62%)	
Yes	14 (28%)	
Spontaneous vanished fetus	5 (10%)	
<b>Number of fetuses reduced</b>		
1 fetus	7 (36.8%)	
2 fetuses	9 (47.4%)	
3 fetuses	3 (15.8%)	
<b>Gestational age for fetal reduction</b>	12.64 $\pm$ 0.74	12.7 ( 11-14)
<b>Mode of delivery</b>		
LSCS	44 (88%)	
Miscarriage	4 (8%)	
ND	2 (4%)	
<b>Indication of delivery</b>		
Emergency	35 (70%)	
Elective	11 (22%)	
Miscarriage	4 (8%)	
<b>PPH</b>		
No	27 (55.1%)	
Yes	22 (44.9%)	
<b>Amount of PPH in ml</b>	1659.1 $\pm$ 958.5	1400 (1000-5000)

Table 2: Outcomes of HOMP.

reduced group was  $30.26 \pm 4.38$ , and  $29.39 \pm 4.78$  weeks for the non-reduced group respectively. Using a T-test to compare the 2 groups we found that there was no statistically significant difference between the reduced and non-reduced groups with a P-value of 0.565, 95% CI (-2.159-3.90), the difference of the mean was found to be 0.87.

**Fetal reduction and postpartum haemorrhage**

Table 3, shows, 84.2% of the group who didn't have fetal reduction had PPH, On the other hand, 15.8% of the group who had fetal reduction had PPH. Using the Chi-square test there is a significant decrease in PPH in the reduced group with a p-value of 0.047

**Maternal co-morbidities**

Women who were fit and healthy without any maternal co-morbidities were 23 (46%) women, and women with 1 or 2 maternal comorbidities were 27 (54%).

Maternal comorbidities included asthma, hypothyroidism, and gestational diabetes, hypertension with pregnancy, iron deficiency anemia, and high body mass index.

**Congenital anomalies**

Congenital anomalies explained in table 4.

**Discussion**

The prevalence of infertility is estimated to be around 9% worldwide. The fact that fertility declines with age, as well as the trend toward later child-bearing, with more women over 30 years of age giving birth, may contribute to an increased number of ART cycles worldwide [13].

After excluding incomplete patients and who lost follow-up, we had 50 women who had HOMP with the mean age of 30 years old. With 74% of them were multiparus (had 1 child or more before).

Multiple births are much more common today than they were in the past, as a result of Assisted Reproductive Technologies. And the associated fetal and maternal complications are significantly high compared to singleton and twins.

Our study demonstrated how ART overwhelmingly contributed to the conception of HOMP with up to 95% conceived through some form of ART, the fact that has been addressed by other authors which their study concurs with our study [14].

HOMP are at extremely high risk for complications and morbidity. The single most important risk factor is preterm

labor. The specter of very early preterm delivery followed by prolonged admission to a neonatal intensive care unit and all the possible sequelae thereof have led some clinicians to offer fetal reduction, even in the absence of known genetic disease or anatomic deformity demonstrated by ultrasound, aiming to reduce the number of fetuses and to prolong the pregnancy to decrease the complications of preterm delivery [15].

In our study, the mean gestational age of preterm delivery was 31 weeks, which is similar to Suri et al. [16].

Clinicians should realize that there are significant emotional challenges for couples undergoing multifetal pregnancy reduction. Many of these couples are long-standing infertility patients who find this procedure opposite to their reproductive desires as they were seeking pregnancy by ART. Furthermore, many couples experience significant moral and ethical dilemmas when considering this technique. It is advisable that adequate psychological evaluation and counselling be initiated before the procedure [15].

It is worth mentioning that fetal reduction did not significantly improve the preterm delivery rate. This is similar to observations made by Alexander, J et al., however, it is different from Abel et al. who concluded fetal reduction in quadruplets is associated with decreased early prematurity and the overall survival is higher after reduction [17,18]. Many factors might contribute to such differences in the studies, including the initial number of fetuses, the maternal comorbidities, and the fact that our study mainly includes those HOMP > triplets, while Abel's study includes only 10 cases of quadruplets.

PPH is cumulative blood loss of greater than or equal to 1000 ml of blood loss [13]. Sequelae of hemorrhage include adult respiratory distress syndrome, shock, disseminated intravascular coagulation, acute renal failure, loss of fertility, and pituitary necrosis ( Sheehan syndrome) [13]. PPH was encountered in almost half of the patients mainly due to overdistension of the uterus which affects the uterine contractions. Fetal reduction however significantly reduced the rate of PPH, which in our opinion is a quite important result, considering the short and long-term risks associated with PPH. In fact, this notion was not specifically addressed in other studies.

For HOMP, vaginal deliveries have been reported, but the problems associated with them suggest that elective caesarean section may be the ideal route of delivery [15]. In our study caesarean section was the mode of delivery in

Fetal reduction Vs PPH		PPH		Total
Fetal reduction		No	Yes	
No	Count	14	16	30
	% Within PPH	56.0%	84.2%	68.2%
Yes	Count	11	3	14
	% Within PPH	44.0%	15.8%	31.8%
Total	Count	25	19	44
	% Within PPH	100.0%	100.0%	100.0%

**Table 3:** Chi-square test of fetal reduction of pregnancy and PPH.



almost 90% of the cases with mean blood loss of (1659.1 ± 958.5 ml), which is another risk of HOMP with all risks during surgery as injury to internal organs, thrombosis, longer hospital stay and the subsequent risks in future pregnancies, including placenta previa and accreta.

The caesarean section should be executed by a team of experienced obstetricians capable of performing a hysterectomy in case of an intractable postpartum hemorrhage. Moreover, an experienced anesthesiologist with sufficient support staff should be available [15].

Table 4, shows the congenital anomalies, we had 2 pregnancies complicated with congenital anomalies, and both pregnancies were monochorionic- diamniotic which is known to increase the risk of congenital anomalies.

Another important point to be addressed is that while abortion has historically raised many ethical issues, it is clear that multifetal pregnancy reduction requires unique ethical consideration due to the fact that fetal reductions aim for a successful birth. Careful reflection about whether this distinction ought to be considered morally relevant or not [19].

Fetal reduction has been an area of great controversy where ethical and legal issues have not been clearly addressed. While individual doctors reserve the right of conscientious objection, one should be aware of the issues surrounding this complex subject matter, so as to be able to better manage and counsel patients. This approach may be applied to similar medical dilemmas with ethical and legal implications [20].

**Strength and Limitations**

There are some limitations to acknowledge, first due to the retrospective character full information about the pre-existing medical condition and pregnancy-related health issues could be incomplete. Secondly, detailed anomaly scans for all the fetuses were difficult to perform so we believe the number of congenital anomalies could be under reported and finally, lack of neonatal data as neonates have separate files and are not linked with the mother’s files.

The major strength of our study is that the women were seen in a tertiary centre, which helped to obtain the data from one source. Additionally, we had high numbers of such rare pregnancies as we didn’t include the triplet pregnancy unlike previous studies in HOMP. Finally, the availability of the

fetal reduction option which helps in making comparisons. In light of the study, further exploration is indicated in the future by well-designed prospective research to address the above issues with a more profound approach.

**Conclusion**

High order multiple pregnancies are a result of modern infertility treatments and have significant serious adverse effects on the mother and the babies.

The ideal treatment for infertility would raise the expectation that high rates of pregnancy which automatically leads to high rates of multiple pregnancies.

Women of HOMP should be counselled about the possible complications associated with carrying the pregnancy and should be provided information about the availability of fetal reduction. There are significant moral, religious and ethical dilemmas when considering fetal reduction. Consequently, it needs an individual approach for each patient considering her psychological status, her religious aspect and to respect her desire in the end. In addition, the clinician should discuss thoroughly with the patient the technical aspects of the procedure.

Patients should be informed that it is a safe procedure in experienced hands but that there will always be a small risk of losing the entire pregnancy.

Although fetal reduction reduced the rate of PPH but did not significantly improve the rate of preterm labour, hence prevention of HOMP is the primary goal.

**Declarations**

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**Competing interest**

The authors have no competing financial or non-financial interests to declare in relation to this article.

**Contribution to authorship**

All authors contributed in planning and conducting the study, SO and AE applied for the approval, MST collected the data ,data analysis done by PC , AE , OA , SO contributed in the interpretation of the data, MST wrote the first draft and revision done by AE, OA, PC and SO

Type of pregnancy	Number of fetuses affected with anomalies	Affected organ	Chorionicity/Amnionicity	Description of anomalies	Outcome
Quadruplets pregnancy	1 fetus	Heart	Monochorionic-diamniotic	2 pulmonary veins draining in the left atrium, dilated right atrium, abnormal tricuspid valve, thick pulmonary valve, with post stenotic dilatation, normal left side heart	Stage III TTTS at 18+ weeks. IUFD for the donor at 29+weeks. Had LSCS at 35+weeks
Quadruplets pregnancy	1 fetus	Head and spine	Monochorionic-diamniotic	With polyhydramnios, lumber Spina bifida and dilated ventricles.	LSCS at 28 weeks

**Table 4:** Congenital anomalies with the description of the anomalies.

All authors approved the final version for submission.

## Ethical approval

The research related to human use has been compiled with all relevant national regulations. Institutional policies and in accordance, with the tenets of the Helsinki declaration. The study has been approved by the local institutional review board at Medical research center (MRC), Hamad Medical Corporation, Doha- Qatar, reference No: MRC0419/2017. Informed consent was waived due to the retrospective design of the study.

To protect patient confidentiality, identifiable information as the name of the patients and health number was excluded from the extracted data and replaced with a specific code generated for the study.

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## Availability of data and materials

The data of the current study are available from the corresponding author on reasonable request.

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