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SELECTIVE FETICIDE – LESSONS LEARNED AND FUTURE CHALLENGES

SELEKTIVNI FETICID – NAUČENE LEKCIJE I BUDUĆI IZAZOV

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Original paper

Key words: multiple pregnancy, high order pregnancy, feticide

SUMMARY. The paper reviews cases of fetal reduction done for high order multi-fetal pregnancies, over a course of four years (2004 – 2008) at Hamad Medical Corporation, in Doha, Qatar. *The aim* is to find out the success of the procedure, its outcome, any related complications to both the mother or the fetuses and whether or not it has any relation to the method of the procedure or the gestational age at which it was done. *Material.* There were seven cases done out of which five were successful. The other two cases declined to have another trial of reduction. Our *results* have shown that fetal reduction is a successful procedure with minimal affection of the fetus and the mother. It also decreases the rate of high order multiple gestation complications and prolongs the pregnancy to near maturity. *Conclusion.* Based on the results of the study the procedure should be offered to all high order gestations.

Izvorni članak

Ključne riječi: blizanačka trudnoća, mnogoplodova trudnoća, feticid

SAŽETAK. Članak prikazuje slučajeve fetalnih redukcija u mnogoplodovih trudnoća, učinjene u četverogodišnjem razdoblju (2004–2008) u Hamad Medical Corporation, Doha, Qatar. *Cilj rada* je prikazati uspjeh postupka, njegov ishod, komplikacije nastale u majke i fetusa, te povezanost postupka s načinom zahvata i ovisnost o dobi trudnoće, u kojoj je zahvat raden. *Materijal.* Ukupno je feticid učinjen u sedam trudnoća. Postupak je u pet bio uspješan; daljnje dvije trudnoće su odustale od ponovljenog zahvata. *Rezultati.* Fetalna redukcija je uspješan postupak, koji neznatno šteti fetusu ili majci. Postupkom se smanjuju mnogoplodne trudnoće te produljuje trudnoća do njene zrelosti za porod. *Zaključak.* Na temelju rezultata studije, postupak bi trebalo ponuditi svim trudnicama s mnogoplodnim trudnoćama.

Introduction

Throughout last four years, during which the fetomaternal unit in Hamad Medical co-operation was founded, diagnosis and intervention had changed dramatically.¹ In a large tertiary centre with 14,000 deliveries a year, with a very active infertility and in-vitro fertilization unit, the incidence of multiple gestations increased dramatically, following the same dramatic increase throughout the world. The rate of triplets live births increasing by 156%, quadruplets by 356% and quintuplets and higher order by 182%. According to Schenker,² the incidence of multiples ranges from a low of 7–9% with clomiphene citrate, to a high of 39% with human menopausal gonadotropins.

More recently, around the world in vitro fertilization centers have specifically aimed at decreasing the multiple pregnancy rates by single embryo transfer procedure. This has not started to be done in Doha yet, but hoping to be implemented, trying to decrease the escalating complications of multiple pregnancies.

Most of the perinatal mortality and morbidity associated with a multifetal pregnancy is related to prematurity and low birth weight.³ In multiple gestations the length of gestation and infant birth weight are inversely proportional to the number of fetuses.⁴

It has been suggested that in multiples the major risk factors for cerebral palsy are preterm birth, intrauterine

growth restriction and intrapartum complications all of which are more common in multiples than in singletons. According to Blickstein and Keith,⁵ the frequency of cerebral palsy bears a significant exponential relationship to the number of fetuses, and iatrogenic multiple births are clearly implicated in the increased cerebral palsy rate. Pharoah⁶ has found the multiple compared with singleton gestations have a five- to tenfold increased risk of cerebral palsy.

It is clear that multiple pregnancies increase the maternal risks in folds. In mothers with triplets was found an incidence of 20% of pregnancy included hypertension, 11–35% of anemia, 35% of postpartum hemorrhage, 24% preterm premature rupture of membranes (PPROM), 9% hemolysis, elevated liver enzymes and low platelets (HELLP), 4% acute fatty liver of pregnancy and 1% of eclampsias.^{7,8}

Materials and methods

First trimester multifetal pregnancy reduction (MFPR) began at the end of 1980's in an attempt to decrease the final number of fetuses. During the last four years we have found that at our hospital we have had seven cases of fetal reduction. As with fetal reduction everywhere, they were all cases of high order multi-fetal pregnancies due to ovulation induction by gonadotrophins, two were accompanied by intra-uterine insemination and one done by in-vitro fertilization.

All the procedures were done transabdominally, by a 20 or 22 gauge needle and using potassium chloride (being the most common agent used) as a feticide agent to stop the heart in asystole.

Multi-fetal reduction should be done from high order pregnancy to either a twin pregnancy or a singleton. Selection reduction of fetuses in the seven cases was not based on genetic evaluation, but mainly on chorionicity and ease of procedure.

Out of the seven cases, six of them were done during the beginning of the second trimester, and the last one was done in the first trimester.

Table 1. Order of gestation in seven cases and number reduced to.
Tablica 1. Redoslijed sedam trudnoća i njihova redukcija.

Number of gestational sacs Broj gestacijskih vrećica	Number of viable fetuses Broj životnih fetusa	Reduced to number Reducirani na broj
5	5	2
7	7	2
4	4	Failed
4	4	3 (patient refused to reduce to 2)
6	4	Failed
5	4	2
7	7	4

Table 2. Method used, attempts and complications of procedure.
Tablica 2. Uporabljene metode, pokušaji i komplikacije postupka.

Method used Rabljen pristup	Volume of KCl Volumen KCl	Number of attempts Broj pokušaja	Reasons of failure Razlog neuspjeha	Complications Komplikacije
Transabdominally	Unknown	1		Nil
Transabdominally	5 ml	1		Nil
Transabdominally	Unknown	2	1 st maternal distress 2 nd refused	Maternal pain
Transabdominally	25 ml	2	1 st fetus moved	Nil
Transabdominally	4 ml	Failed	Painful procedure	Maternal pain
Transabdominally	4 ml	1		Nil
Transabdominally	6 ml	2	1 st to 5 fetuses 2 nd to 4 fetuses	Nil

Table 3. Gestational age at time of procedure.
Tablica 3. Dob trudnoće pri postupku.

Gestational age at presentation (weeks) Dob trudnoće pri prvom kontaktu (tjedni)	Gestational age at procedure (weeks) Dob trudnoće pri zahvatu (tjedni)
12	14
6	13 + 5days
6	14
7	12
7	14
9	14
7	1 st time: 10; 2 nd time:11

After the procedure, the patients were kept under observation for an hour to monitor any uterine contractions, associated with leaking, bleeding or any complication related to the procedure. A repeat ultrasound is done to check viability in the other fetus/es and confirm asystole in the reduced one(s).

Results

During the study period of 4 years, seven patients within reproductive age with multiple pregnancies were included in the study. Our data is shown in the *tables 1 to 4*.

Discussion

Looking through the patients we studied, we found interesting histories and findings. All the seven patients had suffered from infertility for a significant time ranging from one year up to four years, which is the common factor of patients undergoing assisted reproduction techniques. The patients with multifetal pregnancies and their husbands, have three difficult options to choose. Termination of the pregnancy and start a new one which is an unlike choice for a couple who has suffered years of infertility and is probably going through great emotional and financial expenses. A second choice is to continue the high order multiple pregnancy, accepting

Table 4. Maternal complications encountered during pregnancy of the patients.

Number of fetuses Broj fetusa	Maternal complications Komplikacije u trudnoći
2	Preterm labour – Prerani porod
2	Antepartum hemorrhage – Krvarenje prije poroda
4 (maternal pain – bol u majke)	Patient terminated pregnancy Prijevremeno dovršena trudnoća
3	Severe IUGR in twin who shares the placenta with the reduced twin – Teški zastoj rasta dvojka koji je imao udjela u posteljici reduciranog dvojka
4 (failed – neuspjelo)	Severe preeclampsia and post-partum hemorrhage Teška preeklampsija i krvarenje poslije poroda
2	PPROM and preterm labour/PRVP i prerani porod
4	Severe hyperemesis (patient still pregnant) Teška hiperemeza (trudnoća još u tijeku)

Table – Tablica 5. Outcome of pregnancies – Ishod trudnoća.

Number of fetuses Broj fetusa	Gest. age at delivery Dob trudnoće pri porodu	Weight in grams Težina novorođenčeta	Apgar score Apgar zbroj
2	31	1614 1226	6, 9 9, 10
2	36	1850 2275	9, 10 9, 10
4 (patient terminated)	Induced abortion	abortion	abortion
3	32	1076 1326 1405	9, 10 8, 9 9, 10
4	32	1435 1260 740 1320	8, 9 8, 9 5, 10 6, 8
2	33	2295 1930	9, 10 9, 10
4 (patient still pregnant)	Still pregnant	Still pregnant	Still pregnant

Table 6. Mode of delivery of the patients.

Tablica 6. Način poroda trudnica.

Number of fetuses Broj fetusa	Gestational age at delivery Dob trudnoće pri porodu	Mode of delivery Način poroda
2	31	LSCS*
2	36	Normal vaginal delivery
4 (patient terminated pregnancy)	–	–
3	32	LSCS*
5 (failed – neuspjele)	32	LSCS*
2	33	LSCS*
4	Still pregnant – još trudna	Still pregnant – još trudna

* LSCS: low segment cesarean section – carski rez kroz donji segment

the high possibility of having a miscarriage or a very preterm delivery, and the increased risk for perinatal mortality and morbidity. The third option is the multifetal pregnancy reduction, where the number of fetuses is reduced in order to lower the likelihood of preterm delivery and optimize the chance of a successful outcome.⁹

Interestingly enough, one patient was a case of hypogonadotrophic hypogonadism diagnosed since childhood and underwent treatment by IVF. One patient with quadruplets opted to reduce only one fetus to triplets. This patient's fetus shared a placenta with another fetus. Even though it was explained to her in great detail the risks including the risk of feticide of the surviving fetus and intrauterine growth restriction. Due to her beliefs and fear of not having any more children, she insisted upon her point of view. Following up this patient, she actually had two spontaneous pregnancies later on. Another patient with quadruplet pregnancy, in 2004, tried the procedure one, experienced too much pain so was rescheduled. At the next visit, she said she hasn't found

anyone who has heard of this procedure, and owing to the fear of multi-fetal gestation, she opted to terminate her pregnancy at 14 weeks.

The technique of selectively terminate the affected fetus in a multiple pregnancy during the first or second trimester was introduced with different names such as selective reduction, selective termination, selective feticide, selective embryocide, selective abortion, selective birth. In comparison with our cases, the fetal reduction wasn't done selectively, as we don't have the ability of genetic testing and due to selecting the easiest to be done technically.¹⁰

All of the procedures were done transabdominally, fearing complications associated with transvaginal approach as mentioned in the next paragraph. The complications we faced related to the procedure were minimal. Only maternal pain was noted in two patients and the procedure was abandoned to another session.

The first report of first trimester multifetal pregnancy reduction was published in 1986 by Dumez and Oury.¹¹ They presented the first series of selective abortion in multifetal pregnancies, reduced to 4 singletons, 10 set of twins and 1 set of triplets. The procedures were performed by dilating the cervix, and aspirating one or more sacs transvaginally, under ultrasound guidance. Of the 11 completed pregnancies 4 patients delivered at term, three delivered between 33 and 36 weeks, one delivered at 30 weeks and two lost their pregnancies in the second trimester. This technique was quickly abandoned because of high complication rate.

The same year Kanhai and al.¹² reported the reduction of a quadruplet pregnancy to twins, by thoracic puncture under ultrasound guidance. Boulot and al.¹³ published a series of 61 women who had undergone fetal reduction, 35 by transabdominal approach and 26 by transcervical sac perforation and crushing of the embryo if size permitted. Fetal loss rate was 13.1% and preterm labor rate was 56.5%. Since that time the majority of the centers, which perform the technique, utilize transabdominal approach with intrathoracic injection of potassium chloride under ultrasound guidance.

Transabdominal approach is usually performed using the free hand technique without using a needle guide. Six of our patients had the procedure done at the beginning of the second trimester and one was done in the first trimester. The literature reviews say fetal reduction in most centers is performed between 10 and 14 weeks gestation. Before 10 weeks it is technically more difficult because of the small size of the fetuses and greater distance from the maternal abdominal wall to the fetuses. If fetal reduction was performed too late the risk of premature delivery may be higher.⁹

To verify the previous paragraph, Lynch and Berkowitz¹⁴ in 1993, after reporting two hundred completed cases say there is no advantage in delaying the procedure beyond the 12th week of gestation, because if all fetuses are alive and are of appropriate size at that time, spontaneous losses are not likely in the next few weeks.

Moreover the later in pregnancy the termination is performed, the more probable it is that fetal resorption will be incomplete, and may be the rare chance, that maternal disseminated intravascular coagulation will develop. Delay beyond 12 weeks is unnecessary and the risk of miscarriage or preterm rupture of membranes is increased.

The fetus in the lower sac is not reduced, unless it has detectable anomalies or is one twin of a monochorionic set of twins. A 22 gauge, 9 cm long, spinal needle is introduced transabdominal under ultrasound guidance into the fetal thorax in the longitudinal plane and 2–3 mEq potassium chloride (2mEq/mL concentration) is injected slowly so as not to dislodge the needle tip.¹⁵ The cardiac activity is carefully observed for at least 2 minutes and if cardiac activity persists, more potassium chloride is injected. About 0,5 mL of potassium chloride solution is usually sufficient to stop the heart beat. The selection of the fetuses to be reduced is based on the technical ease with which the procedure can be performed. In transabdominal approach the fetus in the sac over the internal cervix os, is left alone unless abnormalities are noted in that fetus. In transabdominal approach it is most common to reduce fetuses located in the middle or upper part of the uterine cavity.

If we look at the rest of the literature, we confirm that the rate of complications is much higher with the transvaginal approach. The first series of ultrasound guided transabdominal reduction with intrauterine potassium chloride injection was reported by Berkowich and al. in 1988.⁹ In that series the first three patients had transcervical procedure while in the rest nine cases the procedure was performed transabdominally with a total loss rate of 33%. In 1999 Mansour et al.¹⁶ reported selective reduction in 46 multiple pregnancies with loss rate 3% and the 81% of the cases delivered after 36 weeks. The experience with the first 200 cases of transabdominal reduction from a single center was reported in 1993.¹⁵ At the time of the procedure, 88 women had triplets, 89 had quadruplets, 16 had quintuplets and seven had six to nine fetuses. Reduction to triplets was done at the patient's request and reduction to singleton was only done for medical indications. The pregnancy loss rates were 7.9% for those with five and 42.9 for those with six or more.

The first collaborative data published in 1993 by Evans and colleagues¹⁷ covered the year from 1988 through early 1991, included all cases performed transabdominally with intrathoracic potassium chloride injection. The second collaborative study in 1994 compared the transabdominal to transcervical approach. The experience on 1000 patients showed a significant decrease in the overall pregnancy loss rate in cases performed transabdominally from 16% to 8% and in the transvaginal/transcervical cases a loss rate of approximately 13%. The prematurity rate between 25–28 weeks' gestation was 5.5%, 10% of the patients delivered at 29–32 weeks and 50% of all patients reached 37 weeks' gestation. It has been also suggested that there is an inverse relation-

ship of starting and finishing number of fetuses to the loss rate.¹⁸

As a trial to find out the optimum procedure, in 1993 Timor-Tritsch and al.¹⁹ reported their experience with 134 patients undergoing fetal reduction by transvaginal puncture and potassium chloride injection. The uncorrected loss rate was 12,6% and there was no difference in the loss rate in those patients whose fetus in the sac over the internal os was targeted for reduction, as opposed to the others. Itskovits and al.¹⁰ also reported two quadruplet pregnancies successfully reduced to twins by transvaginal ultrasound guided aspiration of the gestational sacs. This procedure was similar to transvaginal oocytes retrieval and is performed at an earlier gestational age. The total pregnancy loss rate was 4% at two or less post procedure, 5% at four weeks or less and 16.4% through 24 completed weeks' gestation.¹⁷ The loss rates were 7%, 15% and 30% for patients presenting with triplets, quadruplets and quintuplets respectively and who were reduced to twins. The total loss rate was 14% in patients reduced to twins compared with singletons (25%) and triplets (27%). From these first series could be concluded that:

1. The total pregnancy loss is correlated with the initial and final number of fetuses.
2. Gestational age at delivery is inversely correlated with the initial and final number of fetuses.
3. Gestational age at the time of procedure within the 10–12 weeks has no effect on pregnancy loss. Procedures performed after 12 weeks' gestation may be associated with higher rates of prematurity.
4. Maternal complications have not been reported.
5. Risk of congenital anomalies in survivors is not increased.

The latest collaborative study published in 1996 described 1789 completed pregnancies after fetal reduction.²⁰ The results were obtained from nine centers in five countries. The overall pregnancy loss rate in this study was 11.7% and varied from 7.6% in cases of reduction of triplets to twins and increased to 22.9% for sextuplets to twins.²⁰ Most recently the international collaborative series by Evans et al.²² reported on 3513 cases reduced. All procedures were performed by transabdominal potassium chloride injection, except 331 that were done transvaginally by one group. The overall loss rate was 9.6%, with loss rate varying depending on the starting and finishing number of fetuses. Data by the finishing number of fetuses demonstrated that twins had the best outcomes. Although differences between twins and singletons were small, both groups had significantly lower loss rates than did the group ending with triplets.^{21,22}

In our own study, after the procedure the patient is observed for one hour to monitor for evidence of progressive uterine contraction vaginal bleeding or leakage of amniotic fluid.

The ultrasound examination is repeated in order to confirm normal cardiac activity in the non reduced fe-

tuses, and the asystole in the reduced fetus/es. Following the same rules, we proceeded to do our cases.

Complications that our seven patients encountered were not related to the fetal reduction but related to the risks of multifetal pregnancy. All of the seven patients were presented very early in the pregnancy, during the first trimester, due to complications related to multifetal pregnancy, mostly because of threatened miscarriage and severe hyperemesis gravidarum. This necessitated management and therefore early diagnosis of high order multifetal pregnancy.

Conclusions

Combining our analysis of the seven cases, and the extensive studies that have been published throughout the literature, we have concluded that, over the last 25 years fetal reduction and selective termination have become well accepted procedures to reduce the perinatal mortality and morbidity associated with higher order multiple gestation (MFPR). The gained experience suggests that the transabdominal approach undertaken between 10 and 12 weeks gestation is preferred.

The good pregnancy outcome associated with fetal reduction, chorionic villous sampling before fetal reduction and amniocentesis after fetal reduction are obtained in centers with vast experience with these procedures, with a relatively limited number of operators adhering to a strict common protocol. These procedures should not be generalized to all centers and patients should be extensively counseled for the advantages and disadvantages of the procedure, the risk and the complications.

Although fetal reduction would appear to be of benefit for triplets and higher order gestation, the more logical approach would be prevention of their occurrence through the more judicious use in the future of newer assisted reproductive techniques.

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