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SUCCESSFUL OUTCOME OF 152 HIGH ORDER MULTIFETAL PREGNANCIES AFTER TRANSVAGINAL EMBRYO REDUCTION AND COMPARISON WITH NONREDUCED

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SUMMARY

Objective: *We aimed to assess the safety of transvaginal route for multifetal pregnancy reduction (MPR) early in the first trimester.*

Design: *Retrospective study*

Setting: *Antalya IVF*

Patients: *Hundred and fifty two high order multifetal pregnancies (HOMP) which occurred by assisted reproductive technology (ART) and underwent MPR constituted the study population and 130 primary dichorionic diamniotic ART twins constituted the control group.*

Interventions: *All HOMPs were reduced to twins within 8th week of gestation. Embryo(s) with smaller crown-rump length or with weaker heart activity were preferred to be eliminated. A maximum volume of 2 ml of 2 mEq/ml KCl was injected into the fetal thorax until the cessation of fetal heart movements was observed.*

Main Outcome measures: *The complete pregnancy loss rate*

Results: *The complete pregnancy loss rate <24 weeks of gestation in MPR group and the control group was 6.6% and 6.9% respectively. When outcome parameters were also assessed in relation to the initial number of embryos; complete pregnancy loss rates, vanishing embryo rates, successful pregnancy rates, preterm delivery rates, severe preterm delivery rates, birth weight discordance rates were all similar for the MPR group and the control group. Only one loss out of 152 reduction cases occured within four weeks after MPR.*

Conclusions: *In the present study,. transvaginal route with intrathoraric KCl injection seems to be a safe method for first trimester MPR. Due to its success, safety and possible less psychological burden, we believe that performing the MPR transvaginally at 8th weeks should be the preferred method in ART practice.*

Key words: *assisted reproductive technology, first trimester reduction; multifetal pregnancy reduction; multiple pregnancy; transvaginal embryo reduction*

ÖZET

Multifetal Gebelik Redüksiyonunda (MGR) ilk Trimestirin Erken Döneminde Transvajinal Yaklaşımın Güvenirliği

Amaç: *Multifetal gebelik redüksiyonunda (MGR) ilk trimestirin erken döneminde transvaginal yaklaşımın güvenilirliğini değerlendirmeyi amaçladık.*

Planlama: *Retrospektif çalışma*

Ortam: *Antalya IVF*

Hastalar: *Üremeye yardımcı tedavi (ÜYTE) sonucunda oluşan ve MGR yapılan 152 yüksek çoğul gebelik (YÇG) çalışma grubunu, 130 birincil dikoryonik diamniyotik ÜYTE gebeliği de kontrol grubunu oluşturdu.*

Girişim: *Bütün YÇG'ler 8. gebelik haftasında ikize indirgendi. Baş-popo mesafesi küçük olan veya kalp hareketi zayıf olanlar*

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tercih edildi. Fetal kalp hareketinin durduğu görülene kadar 2 mEq/ml KCl fetal toraks içine enjekte edildi.

Değerlendirme parametreleri: *Tam gebelik kaybı*

Sonuç: *MGR ve kontrol grubunda 24. haftadan once tam gebelik kaybı hızı sırasıyla %6.6 ve %6.9 idi. Değerlendirme parametreleri başlangıçtaki fetus sayısına göre değerlendirildiğinde tam gebelik kaybı, spontan kaybolma (vanishing) hızı, başarılı tamamlanan gebelik hızı, preterm doğum hızı, şiddetli preterm doğum hızı, doğum ağırlığı diskordansı hızı bakımından fark saptanmadı. MGR grubunda sadece 1 hasta işlem sonrası ilk 4 hafta içinde gebeliğini kaybetti.*

Yorum: *Transvaginal yoldan intratorasik KCl enjeksiyonu, ilk trimestir MGR için güvenli bir yöntem olarak görünmektedir. Sonuçların başarılı olması, güveniliriliği ve olası daha az psikolojik yüke neden olması nedenleriyle MGR'yi transvaginal yoldan 8. haftada uygulamak tercih edilmelidir.*

Anahtar kelimeler: *birinci trimestir redüksiyonu; çoğul gebelik; multifetal gebelik redüksiyonu; transvaginal embriyo redüksiyonu; üremeye yardımcı teknikler*

INTRODUCTION

For the past two decades, there has been a worldwide dramatic increase in the incidence of high-order multiple pregnancies (HOMPs). This is due to three main factors: increasing female age at conception; increasing use of ovulation induction agents and the introduction of sophisticated assisted reproduction techniques[1]. HOMPs have dramatically increased rates of fetal complications such as early miscarriages, late abortions, fetal growth retardation[2], extreme prematurity before 32 weeks, low birth weight infants, fetal death in utero and high levels of perinatal mortality and perinatal morbidity[3].

Multiple births account for a disproportionate percentage of the infant mortality rate, estimated at 9.7 per 1000 live births for singletons, 52.7 per 1000 live births for twins and 138.5 per 1000 live births for triplets[4]. Excess perinatal mortality and morbidity associated with HOMPs is mainly due to preterm delivery[5] and the duration of pregnancy is inversely related to the number of fetuses[6]. There are also maternal pregnancy complications associated with HOMPs including preeclampsia, diabetes and postpartum hemorrhage[7].

Multifetal pregnancy reduction (MPR) is the elective reduction of three or more fetuses to a smaller number in an attempt to reduce the incidence of perinatal mortality and morbidity by prolonging gestation. The available data about MPR are quite diverse in terms of technique and timing. Usually confined to the late first and early second trimesters, MPR can be performed transabdominally, transvaginally, or transcervically. At our center we prefer the transvaginal route for MPR at the 8th week of gestation. In this retrospective study, we aimed to assess if early invention by intrathoracic KCl injection via transvaginal route is safe for MPR.

MATERIALS AND METHOD

Patients

Medical records of 152 HOMPs that underwent MPR between March 2000 and September 2004 at Antalya IVF Center were reviewed retrospectively. All of these pregnancies were the result of assisted reproductive technology (ART) procedures. These iatrogenic HOMPs were either referred to our center just for MPR or the result of our own ART treatments. Detailed information was given to all of the patients prior to MPR about the complications of the procedure and the risks of HOMP. A signed informed consent was obtained from each patient before MPR.

One hundred and thirty dichorionic diamniotic primary twin ART pregnancies constituted the control group.

Embryo reduction

All of the MPR procedures were performed under general anesthesia within 8th week of gestation. The patient was sterile draped in lithotomy position; the perineum was cleansed and the vagina was vigorously scrubbed with poviod-iodine. The procedure was done under real-time ultrasonography (Sonoline Adara®, Siemens-Germany) with a 17 gauge-follicle aspiration needle (MDT® Medical Instrument Division BV, The Netherlands) attached to the 7,5 MHz vaginal transducer. Single dose 1 gr. Cephazoline was administered 30 minutes before the operation. Embryo(s) with smaller crown-rump length (CRL) or with weaker heart activity were preferred to be

eliminated. If there is no such a finding, technical ease of accessibility was the criterium for elimination. A maximum volume of 2 ml of 2 mEq/ml potassium chloride (KCl) was injected into the fetal thorax until the cessation of fetal heart movements was observed. The patients were discharged after 1 hour of bed rest. Fetal cardiac activity of the fetuses were controlled by ultrasound before the patients left the hospital. Oral ampicillin + sulbactam 375 mg bid was commenced for 5 days beginning from the evening of the procedure. Ultrasonographic control examination was carried out 1 week after the MPR.

The study was approved by the ethics committee of Antalya IVF.

Outcome parameters

Patients' ages, complete pregnancy loss rates (defined as loss of both fetuses) before 24 weeks of gestation, vanishing embryo rates (defined as complete disappearance of one of the embryos early in pregnancy), successful pregnancy rates (defined as taking home at least one baby), preterm delivery rates (defined as delivery before 37 weeks of gestation), severe preterm delivery rates (defined as delivery before 32 weeks of gestation), birth weights, birth weight discordance rates (birth weight difference >25%), number of fetal anomalies were compared between the reduced group and the control group. Outcome parameters were also assessed in relation to the initial number of embryos.

Postprocedure data of the patients who had antenatal follow-up and delivery elsewhere were requested from the attending physicians via telephone, e-mail or regular mail. Patients with incomplete data were not included in the study.

Student-t test, chi square test, Mann Whitney U test and Kruskal Wallis test were used where applicable.

RESULTS

One hundred and fifty two HOMPs (104 triplets, 34 quadruplets and 14 quintuplets) constituted the study population and 130 primary ART twins constituted the control group. All HOMPs were reduced to twins. All but one procedure were accomplished in a single session. One case needed a second session one week later due to false impression of the severe fetal bradicardia in the first attempt. We encountered chorioamnionitis due to MPR in one triplet which ensued 3 days after the procedure. Combined antibiotherapy with cleocin 600 mg im tid and gentamycin 80 mg im tid was commenced to this case and evacuation of the pregnancy was performed the following day. This is the only pregnancy loss in our series which occured within four weeks of MPR (1/152[0.6%]). The case responded antibiotherapy well and cure was succeeded within 5 days. The same patient became pregnant 3 months later following ICSI again and delivered healthy twins at term abdominally. Age of the patients and overall complete pregnancy loss rate before 24 gestational weeks were similar for both groups (Table I). The incidence of post surgical vanishing embryo in MPR group was 7.9% (12/152)

Table I: *Demographic and pregnancy outcome parameters*

	MPR group (no:152)	Control group (no:130)	p
Age	28.4± 4.3	29.9± 4.4	>0.05*
Pregnancy loss within 4 weeks of MPR	1/152 (%0.6)	-	NA
Overall complete pregnancy loss<24 weeks of gestation	10/152(6.6%)	9/130(6.9%)	>0.05 •
Vanishing embryo	12/152(7.9%)	15/130(11.5%)	>0.05 •
Successful pregnancy	110/123(89.4%)	97/108(89.8%)	>0.05 •
Preterm delivery	26/110(23.6%)	29/108 (26.8%)	>0.05 •
Severe preterm delivery	14/110(12.7%)	7/108 (6.4%)	>0.05 •
Birth weight	2250(1822-2500)	2400(2135-2700)	<0.05‡
Birth weight discordance in twin births	18/82(21.9%)	14/73(18.5%)	>0.05 •
Fetal anomalies	2/184(1.1%)	2/176(1.1%)	>0.05 •

NA: not applicable

**Student-t*

•χ^2 *test*

‡*Mann Whitney U*

Ψ *29 Gestations in MPR group and 22 pregnancies in control group are >24 weeks of gestation and ongoing.*

and all occurred in 9th and 10th gestational weeks. One of these vanishing twin patients miscarried the co-twin in 16th gestational week and 11 patients took home one healthy baby. In control group, 15 patients (11.5%) had a vanishing embryo all between 9-13 weeks of pregnancy. One of these pregnancies was lost due to preterm premature rupture of membranes at 20th weeks of gestation, 14 patients took home one healthy baby. Fetal demise of co-twin in utero (defined as death of one embryo >13 weeks) occurred in two patients from MPR group both in 26th weeks of gestation. Three patients from the reduced group and two patients from the control group delivered between 24-28 weeks and lost both twins perinatally.

One hundred and ten reduced pregnancies were successfully completed. There were two malformations in MPR group: one baby has atrial septal defect and one infant has talipes foot. Twenty nine pregnancies are over 24 weeks of gestation and ongoing at the moment. Among the primary twin pregnancies which constituted the control group, 97 were successfully completed. One of the babies in control group had isolated dextrocardia and another one had trisomy 18. This latter baby died in perinatal period. Twenty two pregnancies in control group are over 24 weeks of gestation and ongoing at the moment.

The preterm delivery rates, severe preterm delivery rates, birth rate discordance rates were similar in both groups ($p>0.05$) while birth weight of the MPR group was significantly lower than primary twin group ($p<0.05$). When outcome parameters were also assessed in relation to the initial number of embryos; pregnancy loss rates and delivery outcome did not change in relation to the initial number of embryos (Table II). Numbers of uterine penetrations were as follows: 6 penetrations in 2 patients, 4 penetrations in 3 patients, 3 penetrations in 9 patients, 2 penetrations in 28 patients and single penetration in the others. The case in which the pregnancy loss occurred within 4 weeks after the procedure had single puncture.

DISCUSSION

IVF and ICSI data collected from 18 European countries shows that although ≥4 embryos are transferred in 9.4% of the cycles, this proportion is higher for some eastern and southern European countries (ranging from 25.8% to 54.7%)[8]. The international rates of triplet or higher order pregnancies after assisted reproduction are 7.3% at conception[9]. Recent annual report by ESHRE also revealed that HOMPs constitutes 2.04% of all ART deliveries[10] and this rate remain unchanged during the last 4 years. Hence, the management of HOMPs still represents a true challenge. MPR is one of the options for the improvement of the outcome of HOMPs. However optimal route and the method of embryo reduction have not been completely clarified yet.

The maternal and fetal benefits of performing MPR in women with four or more fetuses is well established [11,12]. Although contradictory reports exist, several studies also reveal that reduction of triplets to twins is effective in improving preterm birth and fetal growth and overall the rate of pregnancy loss[3,13-16]. In addition, studies comparing the post-MPR twins with nonreduced dichorionic twins did not show an increase in the rates of birth weight discordance and intrauterine growth restriction unless the starting fetal number is > or = 5[17,18]. The loss rate of the nonreduced triplets was 25%, compared with a loss rate of approximately 6% in both the post-MPR twins and nonreduced twins[16]. MPR not only improve the obstetric outcomes for pregnancies with multiple gestations but also is associated with significant fiscal savings[19]. We believe that one should also account

Table II: *Pregnancy loss rates of reduced pregnancies in relation to the initial number of embryos*

	Triplets	Quadruplets	Quintuplets	P*
No of patients	104	34	14	NA
Vanishing embryo	7/104 (6.7%)	3/34(8.8%)	2/14 (14.2%)	>0.05
Pregnancy loss<24 weeks	7/104(6.7%)	2/34(5.8%)	1/14(7.1%)	>0.05
Successful pregnancy	67/74(90.0%)	30/34(88.2%)	13/15(68.6%)	>0.05
Preterm delivery	17/67(25.4%)	6/30(20.0%)	3/13(23.0%)	>0.05
Severe preterm delivery	7/67(10.4%)	5/30(16.6%)	2/13(15.3%)	>0.05
Birth weight discordance	11/49 (22.44%)	5/22(22.72%)	2/11(18.18%)	>0.05

NA: not applicable

**Kruskal Wallis ANOVA test*

the availability as well as the quality of the neonatal intensive care provided before deciding the triplets to deliver. Since the quality and the availability of the neonatal care facility may differ between countries and the regions our common practice in triplets is referring the patient to fetal reduction.

MPR can be performed by transabdominal (TA), transvaginal (TV) or transcervical (TC) routes. Currently the former techniques are common in practice and transcervical technique is nearly abandoned due to high complication rates including chorioamnionitis and abortions[20]. Timing of the procedure also changes from selective fetocide in the second trimester[21-23] to early transvaginal interventions[24-27]. Transvaginal route can also be performed by three different ways: by embryo puncture-only[24], by embryo aspiration (25,26), or intracardiac injection of KCl[27]. Pregnancy loss rates of TA, TV and TC approaches in MPR generally ranges between %5.4 and %33.3[23,27-33]. In a review of the 1993-1996 literature, the total pregnancy loss rate was found to be 12.3%, one third of which occured within four weeks from the procedure [11]. In another review, Dechaud et al reported total fetal loss rates as 16.7% for the transabdominal, 24.8% for the transcervical and 10.9% for the transvaginal route[20]. In a collaborative study of 1789 reductions, Evans et al reported a loss rate of 13% for TC and TV routes and 8-16% for TA route[34]. In the most recent collaborative series Evans et al reported 3513 cases from five countries with an overall loss rate of 9.6% and stressed the importance of technical experience as with increasing experience there has been a considerable improvement in outcomes[18].

In the present study, complete pregnancy loss rate before 24th weeks of gestation in MPR group was one of the lowest in the literature and it is not significantly different from that of the control group (6.6% and 6.9% respectively, p>0,05). Spontaneous loss rate for primary twins was reported as 9.5% by a previous study[35]. Within four weeks after the procedure only one loss occurred in our series (0.6%). As the majority of the pregnancy losses occur within four weeks of the procedure[11], and the loss rates<24 weeks of gestation are similar for our MPR and control groups, only this single lost case can definitely be attributed directly to the MPR procedure. This only loss soon after MPR due to chorioamnionitis was the third MPR case in our series. This unfortunate experience indicated us to make a meticulous anticeptic preparation before transvaginal approach.

One crucial question is why early intervention seems to be more successful for reduction. In our study we perform the reduction when the CRL is 10 mm on avarage compared to 50 mm to 70 mm for transabdominal approach. This 5 to 7 times increase in two dimensional view corresponds to 25-50 increase in the volume of the fetus that is left for absorption. We believe that the left over volume is crucial and therefore this little volume may contribute to the successful outcome since the eliminated material to be resorbed is smaller.

Recently two studies suggested TV aspiration as a modified method. Mansour et al reported relatively higher (8.8%) fetal loss rate[26] while in series of Coffler et al 7% of cases needed a second session to accomplish the procedure[25]. A relatively novel modification of TV technique namely cardiac puncture also revealed similar pregnancy loss rate (7.3%) compared to ours[24]. According to our experience it seems to be technically difficult to penetrate the heart of a fetus with a CRL of 1-1.5 cm. Therefore we believe that the possible mechanism of elimination in our technique is the combination of both infiltration of the intrathoracic KCL into the pericardiac region and the mechanical trauma by the needle itself.

Current literature data show that: pregnancies over triplets have higher loss rates[11,18,36]. In addition, birth weight discordance between surviving twins was increased with greater starting number[18]. But our data do not support these results. Vanishing embryo rates, pregnancy loss rates, successful pregnancy rates, preterm delivery and severe preterm delivery rates and birth weight discordance rates were all similar for triplets, quadruplets and quintuplets in our study. Dechaud et al also reported similar loss rates in various starting numbers in their review[20].

The incidence of “vanishing embryo phenomenon” which is the complete disappearance of one of the embryos early in pregnancy occurs in 16% to 43% of all multiple ART pregnancies[37,38]. In the present study vanishing embryo rates were similar in MPR (7.9%) and control (11.5%) groups (p>0.05). Previous reports about MPR also revealed similar low vanishing embryo rates as 3-5.4%[3,24]. The explanation of this low incidence may be the elimination of the embryo(s) with smaller CRL or weaker heart activity since the

fetus with the smaller CRL has a greater chance of spontaneous demise[39]. In addition, it is also well known that 80-90% of spontaneous resorptions occur before 9 weeks[24,40] and almost none beyond the 14th week[41]. MPR solely does not seem to increase the vanishing embryo rate.

We found similar successful pregnancy rates for reduced twins and primary twins ($p>0.05$). Furthermore both the reduced twins and the primary twins have similar incidence of preterm delivery rates. The incidence of 23.6% after MPR in the present study was similar to those reported by others (20.7%-57.8%)[42,43]. Audibert et al reported multifetal pregnancy reduction as an independent risk factor for twin birth weight discordance in 346 dichorionic twins[44]. However in our series, birth weight discordance rate was not higher for the MPR group. We believe that by performing the procedure earlier in fetal life might have a positive effect on this complication.

Current belief suggests that performing the MPR during the second trimester may provide an advantage in terms of selecting the fetus(es) with thicker nuchal translucency for elimination and reduce the risk of encountering chromosomal abnormality. Hence, risk of overlooking an abnormal embryo as well as theoretical complications of general anesthesia and infection can be listed as the risks of our technique. On the other hand early transvaginal intervention may provide the chance of elimination of the fetus(es) with smaller CRL as the average CRL gestation in the aneuploid population was less than that derived from the LMP[45]. In addition, some karyotype abnormalities (trisomy 18 and triploidy) are associated with fetal bradycardia[46]. Hence, by eliminating the embryos with smaller CRL or weaker heart rates, we may probably be choosing the high-risk embryos for chromosome abnormality. We have not encountered any chromosomal abnormalities in our series in the MPR group.

In spite of the successful results of MPR, this procedure is not a part of reproduction management, but just a practice to help infertile couples in prevention of the unwanted effects of HOMPs. The goal of a successful ART treatment is a singleton pregnancy or at least avoiding HOMPs and reducing the number of embryos transferred should be the main approach for this goal [47]. But in certain circumstances MPR is a life boat procedure.

We conclude that transvaginal route with intrathoraric KCl injection is a safe and effective method for first trimester MPR. Transvaginal route has several advantages: i)Early TV intervention has a satisfactory outcome for the children and limited (almost no) risks for the mother ii) IVF practitioners are more familiar with TV route and equipment than TA route iii) Penetration of several gestational sacs without withdrawing the needle from the uterus may be possible iv) It is easier for couples to accept MPR and no serious psychyatric morbidity is detected after TVMPR[48].

REFERENCES

1. Brinsden PR. Controlling the high order multiple birth rate: the European perspective. Reprod Biomed Online. 2003; 6(3): 339-344.
2. Boulot P, Hedon B, Pelliccia G, Deschamps F, Benos P, Audibert F et al. Obstetrical results after embryonic reductions performed on 34 multiple pregnancies. Hum Reprod 1990; 5: 1009-1013.
3. Boulot P, Vignal J, Vergnes C, Dechaud H, Faure JM, Hedon B. Multifetal reduction of triplets to twins: a prospective comparison of pregnancy outcome. Hum Reprod 2000; 15(7): 1619-23.
4. Jewell SE, Yip R. Increasing trends in plural births in the United States. Obstet Gynecol 1995; 85: 229- 232.
5. Lipitz S, Frenkel Y, Wats C, Ben-Rafael Z, Barkai G, Reichman B. High-order multifetal gestation- management and outcome. Obstet Gynecol 1990; 76: 215-18.
6. Alvarez M, Berkowitz R. Multifetal gestation. Clin Obstet Gynecol 1990; 33: 79-87.
7. Stone J, Eddleman K. Multifetal pregnancy reduction. Curr Opin in Obstet Gynecol 2000; 12: 491-96.
8. Nygren KG, Andersen AN; The European IVF-monitoring programme (EIM). Assisted reproductive technology in Europe, 1998. Results generated from European registers by ESHRE. European Society of Human Reproduction and Embryology. Hum Reprod 2001; 16(11): 2459-71.
9. Cohen J. How to avoid multiple pregnancies in assisted reproduction. Hum Reprod 1998; 13 Suppl 3: 197-214.
10. Andersen AN, Gianaroli L, Nygren KG; The European IVF-monitoring programme; European Society of Human Reproduction and Embryology. Assisted reproductive technology in Europe, 2000. Results generated from European registers by ESHRE. Hum Reprod 2004; 19(3): 490-503.
11. Fasouliotis SJ, Schenker JG. Multifetal pregnancy reduction: a review of the world results for the period 1993-1996. Eur J Obstet Gynecol Reprod Biol 1997; 75(2): 183-190.

12. Berkowitz RL, Lynch L, Stone J, Alvarez M. The current status of multifetal pregnancy reduction. Am J Obstet Gynecol 1996; 174(4): 1265-72.
13. Stone J, Berkowitz RL. Multifetal pregnancy reduction and selective termination. In: Multiple pregnancy delivery. Gall SA (editor). St Louis Missouri, USA. Mosby-Year Book Inc.; 1996: 181-197.
14. Boulot P, Hedon B, Pelliccia G, Peray P, Laffargue F, Viala JL. Effects of selective reduction in triplet gestation: a comparative study of 80 cases managed with or without this procedure. Fertil Steril 1993; 60(3): 497-503.
15. Kadhel P, Olivennes F, Fernandez H, Vial M, Frydman R. Are there still obstetric and perinatal benefits for selective embryo reduction of triplet pregnancies? Hum Reprod 1998; 13 (12): 3555-59.
16. Yaron Y, Bryant-Greenwood PK, Dave N, Moldenhauer JS, Kramer RL, Johnson MP, Evans MI. Multifetal pregnancy reductions of triplets to twins: comparison with nonreduced triplets and twins. Am J Obstet Gynecol 1999; 180(5): 1268-1271.
17. Lipitz S, Uval J, Achiron R, Schiff E, Lusky A, Reichman B. Outcome of twin pregnancies reduced from triplets compared with nonreduced twin gestations. Obstet Gynecol 1996; 87 (4): 511-514.
18. Evans MI, Berkowitz RL, Wapner RJ, Carpenter RJ, Goldberg JD, Ayoub MA, Horenstein J, Dommergues M, Brambati B, Nicolaides KH, Holzgreve W, Timor-Tritsch IE. Improvement in outcomes of multifetal pregnancy reduction with increased experience. Am J Obstet Gynecol 2001; 184 (2): 97-103.
19. Miller VL, Ransom SB, Shalhoub A, Sokol RJ, Evans MI. Multifetal pregnancy reduction: perinatal and fiscal outcomes. Am J Obstet Gynecol 2000; 182(6): 1575-1580.
20. Dechaud H, Picot MC, Hedon B, Boulot P. First-trimester multifetal pregnancy reduction: evaluation of technical aspects and risks from 2,756 cases in the literature. Fetal Diagn Ther 1998; 13 (5): 261-265.
21. Kahraman S, Vicdan K, Nuhoglu A, Danisman N, Isik Z, Ozgun OD, Biberoglu K Outcomes of multifetal pregnancy reduction in multiple pregnancies achieved by intracytoplasmic sperm injection using ejaculated, testicular, or epididymal sperm. Gynecol Obstet Invest 1997; 44 (1): 1-5.
22. Kanhai HH, de Haan M, van Zanten LA, Geerinck-Vercammen C, van der Ploeg HM, Gravenhorst JB. Follow-up of pregnancies, infants, and families after multifetal pregnancy reduction. Fertil Steril 1994; 62(5): 955-959.
23. von Dadelszen P, Johnson JA, Farquharson DF, Wilson RD, Seaward PG. Multifetal pregnancy reduction and selective termination: the Canadian experience. Fetal Diagn Ther 1999; 14 (6): 360-364.
24. Ibérico G, Navarro J, Blasco L, Simón C, Pellicer A and Remohí J. Embryo reduction of multifetal pregnancies following assisted reproduction treatment: a modification of the transvaginal ultrasound-guided technique. Hum Reprod 2000; 15: 2228-2233.
25. Coffler MS, Kol S, Drugan A, Itskovitz-Eldor J. Early transvaginal embryo aspiration: a safer method for selective reduction in high order multiple gestations. Hum Reprod 1999; 14(7): 1875-1878.
26. Mansour RT, Aboulghar MA, Serour GI, Sattar MA, Kamal A, Amin YM. Multifetal pregnancy reduction: modification of the technique and analysis of the outcome. Fertil Steril. 1999; 71(2): 380-384.
27. Lipitz S, Yaron Y, Shalev J, Achiron R, Zolti M, Mashiach S. Improved results in multifetal pregnancy reduction: a report of 72 cases. Fertil Steril 1994; 61(1): 59-61.
28. Boulot P, Hedon B, Pelliccia G, Lefort G, Deschamps F, Arnal F, Humeau C, Laffargue F, Viala JL. Multifetal pregnancy reduction: a consecutive series of 61 cases. Br J Obstet Gynaecol 1993; 100(1): 63-68.
29. Evans MI, Dommergues M, Timor-Tritsch I, Zador IE, Wapner RJ, Lynch L, Dumez Y, Goldberg JD, Nicolaides KH, Johnson MP, et al. Transabdominal versus transcervical and transvaginal multifetal pregnancy reduction: international collaborative experience of more than one thousand cases. Am J Obstet Gynecol 1994; 170(3): 902-909.
30. Donner C, McGinnis JA, Simon P, Rodesch F. Multifetal pregnancy reduction: a Belgian experience. Eur J Obstet Gynecol Reprod Biol 1991; 25; 38(3): 183-7.
31. Lipitz S, Grisaru D, Achiron R, Lidor A, Mashiach S, Schiff E. Pregnancy outcome after early amniotic fluid leakage after transabdominal multifetal reduction. Fertil Steril 1996; 65 (5): 1055-1058.
32. Brambati B, Tului L, Baldi M, Guercilena S. Genetic analysis prior to selective fetal reduction in multiple pregnancy: technical aspects and clinical outcome. Hum Reprod 1995; 10(4): 818-825.
33. Stone J, Eddleman K, Lynch L, Berkowitz RL. A single center experience with 1000 consecutive cases of multifetal pregnancy reduction. Am J Obstet Gynecol. 2002; 187(5): 1163-1167.
34. Evans MI, Dommergues M, Wapner RJ, et al. International, collaborative experience of 1789 patients having multifetal pregnancy reduction: a plateauing of risks and outcomes. J Soc Gynecol Invest 1996; 3: 23-26.
35. Antsaklis AJ, Drakakis P, Vlazakis GP, Michalasa S. Reduction of multifetal pregnancies t o twins does not increase obstetric or perinatal risks. Hum Reprod 1998; 14: 1338-1340.

36. The ESHRE Capri Workshop Group. Multiple gestation pregnancy: Review. Hum Reprod 2000; 15(8): 1856-1864.
37. Seoud MA, Toner JP, Kruithoff C, Muasher SJ. Outcome of twin, triplet and quadruplet in vitro fertilization pregnancies: the Norfolk experience. Fertil Steril 1992; 57: 825-834.
38. Bollen N, Camus M, Tournaye H, Wisanto A, Van Steirteghem AC, Devroey P. Embryo reduction in triplet pregnancies after assisted procreation: a comparative study. Fertil Steril 1993; 60: 504-509.
39. Kol S, Levron J, Lewit N, Drugan A, Itskovitz-Eldor J. The natural history of multiple pregnancies after assisted reproduction: is spontaneous fetal demise a clinically significant phenomenon? Fertil Steril 1993; 60: 127-130.
40. Manzur A, Goldsman MP, Stone SC, Frederick JL, Balmaceda JP, Asch RH. Outcome of triplet pregnancies after assisted reproductive techniques: how frequent are the vanishing embryos? Fertil Steril 1995; 63: 252-257.
41. Manzur A, Goldsman MP, Stone SC, Frederick JL, Balmaceda JP, Asch RH. Outcome of triplet pregnancies after assisted reproductive techniques: how frequent are the vanishing embryos? Fertil Steril 1995; 63(2): 252-257.
42. Shalev J, Frenkel Y, Goldenberg M, Shalev E, Lipitz S, Barkai G, et al. Selective reduction in multiple gestations: pregnancy outcome after transvaginal and transabdominal needle-guided procedures. Fertil Steril 1989; 52: 416-420.
43. Itskovitz-Eldor J, Drugan A, Levron J, Thaler I, Brandes JM. Transvaginal embryo aspiration- a safe method for selective reduction in multiple pregnancies. Fertil Steril1992; 58: 351- 355.
44. Audibert F, Boullier M, Kerbrat V, Vial M, Boithias C, Frydman R. [Growth discordance in dichorionic twin pregnancies: risk factors, diagnosis and management] J Gynecol Obstet Biol Reprod 2002; 31 Suppl 1: 2S15-24.
45. Macintosh MC, Brambati B, Chard T, Grudzinskas JG. Crown-rump length in aneuploid fetuses: implications for first-trimester biochemical screening for aneuploidies. Prenat Diagn 1995; 15 (8): 691-694.
46. Liao AW, Snijders R, Geerts L, Spencer K, Nicolaides KH. Fetal heart rate in chromosomally abnormal fetuses. Ultrasound Obstet Gynecol 2000; 16(7): 610-613.
47. American College of Obstetrics and Gynecology Committee on Ethics. Nonselective embryo reduction: ethical guidance for the obstetrician-gynecologist. ACOG Committee Opinion No. 215. April 1999
48. Bergh C, Moller A, Nilsson L, Wikland M. Obstetric outcome and psychological follow-up of pregnancies after embryo reduction. Hum Reprod 1999; 14(8): 2170-2175.