

PATRÍCIA ALMEIDA¹ANA PATRÍCIA DOMINGUES¹ADRIANA BELO²ETELVINA FONSECA¹PAULO MOURA^{1,3}

Triplet pregnancies: perinatal outcome evolution

Evolução dos resultados perinatais em gestações triplas

Original Article

Keywords

Pregnancy, triplet
Triplets
Embryo transfer
Fetal reduction, multifetal

Palavras-chave

Gravidez de trigêmeos
Trigêmeos
Transferência embrionária
Redução de gravidez multifetal

Abstract

PURPOSE: To evaluate the obstetric and perinatal outcomes evolution of triplet pregnancies. **METHODS:** A prospective observational study was conducted in triplet pregnancies delivered over 16 years in a tertiary obstetric center with differentiated perinatal support. Evaluation of demographic factors, obstetric complications, gestational age at delivery, mode of delivery, birth weight and immediate newborn outcome were done over a 16 years period. A global characterization of the sample was performed considering the listed parameters. Variables were categorized in three groups according to year of occurrence: 1996–2000, 2001–2006, 2007–2011, and all parameters were compared. **RESULTS:** Of the 33 triplets included, 72.7% resulted from induced pregnancies. All except one patient received prenatal corticosteroids and five received tocolytics. All women delivered prenatally and no significant differences were seen in the mean gestational age at delivery or birth weight towards time. There were three intrauterine fetal deaths. Neonatal immediate outcomes were not significantly different over the years. **CONCLUSION:** Despite remarkable progresses in perinatal and neonatal cares, no noticeable impact in triplet gestations' outcomes was seen, sustaining that triplets should be avoided due to their great risk of prematurity and neonatal morbidities, either by limiting the numbers of embryos transferred or by fetal reduction.

Resumo

OBJETIVO: Avaliar a evolução obstétrica e os resultados perinatais das gestações triplas. **MÉTODOS:** Um estudo observacional prospectivo foi realizado em gestações triplas durante 16 anos num centro obstétrico terciário com apoio perinatal diferenciado. Foram realizadas avaliações dos fatores demográficos, de complicações obstétricas, da idade gestacional ao parto, do tipo de parto, peso do recém-nascido e resultado neonatal imediato por um período de 16 anos. A caracterização global da amostra foi realizada considerando os parâmetros listados. As variáveis foram divididas em três grupos de acordo com o ano de ocorrência: 1996–2000, 2001–2006, 2007–2011, e todos os parâmetros foram comparados. **RESULTADOS:** Das 33 gestações triplas incluídas, 72,7% resultaram de gravidezes induzidas. Exceto uma paciente, todas receberam corticosteroides pré-natal e cinco efetuaram tocolíticos. Todas as mulheres tiveram um parto pré-termo e não se observaram diferenças significativas na idade gestacional média ao parto nem no peso ao nascer ao longo do tempo. Houve três óbitos fetais. Os resultados neonatais imediatos não foram significativamente diferentes ao longo dos anos. **CONCLUSÃO:** Apesar dos avanços notáveis em cuidados perinatais e neonatais, nenhum impacto perceptível nos resultados de gestações triplas foi verificado. Essas gestações devem ser evitadas devido ao grande risco de prematuridade e morbidade dos recém-nascidos, tanto por limitação do número de embriões transferidos como por redução fetal.

Correspondence

Ana Patrícia Rodrigues Domingues
Maternidade Dr Daniel de Matos – Serviço de Obstetria A,
Hospitais da Universidade de Coimbra
Rua Miguel Torga, 3030 – 165
Coimbra, Portugal

Received

06/19/2014

Accepted with modifications

07/23/2014

DOI: 10.1590/S0100-720320140005066

Serviço de Obstetria A da Maternidade Dr. Daniel de Matos do Centro Hospitalar e Universitário de Coimbra – Coimbra, Portugal.

¹Obstetrics-A Department, Maternidade Dr. Daniel de Matos, Centro Hospitalar e Universitário de Coimbra – Coimbra, Portugal.²Master of Science in Biostatistics – Coimbra, Portugal.³Obstetrical Clinic, Faculdade de Medicina, Universidade de Coimbra – Coimbra, Portugal.

Conflicts of interests: none.

Introduction

The incidence of multiple gestations, particularly triplet and higher order pregnancies, has considerably increased over the past three decades, mainly due to the current widespread practice of assisted reproductive technology (ART), but also to the trend of delayed childbearing¹⁻³. This increase in multiple gestations is known to cause concern in contemporary obstetrical practices because these pregnancies are known to be associated to poorer maternal and perinatal outcomes. The risk of adverse neonatal outcome undoubtedly increases with the expansion of fetuses' number, mainly as a result of preterm birth and/or low birth weight².

In triplet pregnancies, the incidence of overall preterm deliveries is approximately 90%, with a risk of extreme preterm birth <28 weeks and very preterm birth 28–32 weeks 13-fold and almost 20-fold, respectively, when compared to singletons⁴. The rate of preterm births before 32 weeks of gestation in triplets is 3.3-fold higher than in twins and 24.1-fold higher than in singletons³.

Along with clinical risks, both for mothers and for fetus/neonates, we should not ignore relevant increasing medical costs on the health care system associated with high order multiple pregnancies. It has been reported that expenses are almost four times higher for triplet pregnancies compared with singleton pregnancy³. Fortunately, despite a continuing expansion in the number of treatment cycles reported on ART for Europe, the number of multiple embryo transfers 3+ embryos and the multiple delivery rate have shown a clear decline, resulting in remarkable reduction of triplet deliveries 3.6% in 1997 and 0.8% in 2009⁴.

The authors' purpose was to evaluate obstetric, maternal and perinatal outcomes of triplet pregnancies over a 16 year period to detect any progress in these results over the years.

Methods

Data from files of all triplet pregnancies which were delivered in our tertiary obstetric center with differentiated perinatal support over a period of 16 years between January 1996 and December 2011 were prospectively collected and analyzed in this cohort observational study. No intervention was done beside the normal triplet surveillance protocol of our center. This study was included in an investigation project approved by the Ethics Committee of the University Hospitals of Coimbra.

All triplet pregnancies independently of chorionicity spontaneously conceived and obtained by assisted reproduction techniques were included.

Obstetric complications included in this study were first trimester bleeding; urinary, genital or other infections; anemia; fetal malformations; hypertensive diseases of the pregnancy; Gestational hypertension, preeclampsia, eclampsia and HELLP syndrome; gestational diabetes (GD); preterm delivery (PTD), considered delivery occurred after 24 and before 37 weeks of gestation; preterm premature rupture of membranes (PPROM), considered the occurrence of premature rupture of membranes after 24 and before 37 weeks of gestation; twin-to-twin transfusion syndrome (TTTS), intrauterine growth restriction (IUGR), defined as fetal measure of abdominal perimeter <10th centile and discordant growth restriction, defined as 20% difference between fetal birthweight and fetal death.

About birth, gestational age at delivery were categorized in the following classes: <28, 28–32, 33–34, 35–36 and >36 weeks. The mode of delivery was categorized as vaginal or cesarean, birthweight, Apgar's score at first and fifth minute and admission of the neonates in the Neonatal Intensive Care Unit were analyzed.

Neonatal immediate mortality and morbidity were also considered, the last being categorized in global, respiratory, infectious and neurological. Puerperal complication occurrences were also analyzed, namely anemia, hemorrhage, hypertension complications, endometritis.

Gestational age was calculated from the data of embryo transfer for the induced pregnancies obtained from ART, and from the last menstrual period in the spontaneously conceived group, both confirmed and corrected by the time of the first trimester ultrasound. Chorionicity was also determined in the first trimester scan by lambda and T signs.

A global characterization of the sample was performed considering the above listed parameters. Due to the small number of cases we categorized variables in three groups according to year of occurrence: 1996–2000, 2001–2006, 2007–2011.

For categorial variables, the correlation between groups defined by year, gestational age variables at delivery and birth weights of the three newborns was evaluated by the Kruskal-Wallis test. In each group, these variables were described by mean, standard deviation, quartiles, minimum and maximum. In the case of variables related to each obstetric complication and newborn morbidities, their occurrence in the three groups was evaluated by χ^2 test for Trend. For numeric variables, the correlation between groups defined by

year and gestational age variables at delivery and birth weights of the three newborns was evaluated by estimating the Spearman correlation coefficient and it has been represented by a scatter plot. The significance level used in this analysis was 5%. The statistical software SPSS® v19.0.0.2 was used.

Results

During the period of this study (from January 1996 to December 2011) there were 33 triplet pregnancies identified: 28 trichorionic triamniotic (TT), 4 dichorionic triamniotic (DT), and 1 monochorionic triamniotic (MT). Twenty-four of these were induced pregnancies. The distribution of the results along the three groups formed is seen in Tables 1 and 2.

Globally, 27 women were nulliparous and the mean maternal age had an increasing tendency (Table 1). One

woman reported first trimester bleeding. Anemia was diagnosed in two, both during the third trimester. There were five cases of urinary tract infection. Four women had GD and four pregnancies induced hypertension disorders. Maternal hospitalization in the antenatal period occurred in 30.3%. There were no congenital malformations. IUGR complicated four pregnancies and discordant growth restriction, one. One pregnant experienced TTTS MT placentation. PPROM rate was 9.1%. Prenatal corticosteroids for fetal lung maturation were administered in 96.9% and 5 women received tocolytics. The total number of intrauterine fetal death was three, two fetuses were in a MT pregnancy with TTTS, and the other in one dichorionic triamniotic pregnancy.

All women had a PTD and a cesarean section was performed in 32 pregnancies (Table 1). Neonatal data results are resumed in Table 2. Gestational age at delivery and fetuses birthweight distribution and evolution over the period analyzed stayed stable over the years.

Postpartum hemorrhage occurred in three patients, all of those requiring blood transfusion. Puerperal anemia was documented in six women. There was one hypertensive complication registered in the puerperium.

Table 1. Obstetrical results of triplets over the three groups period between 1996 and 2011

	1996–2000 n=12	2001–2006 n=12	2007–2011 n=9
Mean maternal age (years)	27.3±5.9	33.3±4.6	31.1±3.3*
Induced pregnancies (n)	7	10	7
Complications (n)	11	10	8
1 st trimester bleeding	0	0	1
Anemia	1	1	0
Infections	2	1	2
Hypertension induced by pregnancy	1	2	1
Gestational diabetes	1	2	1
PPROM	2	1	0
Fetal malformations	0	0	0
IUFD	2 [†]	0	0
Mono/dichorionicity	3	0	2
TTTS	1	0	0
IUGR	2	1	1
Growth discordance 20%	0	0	1
Therapeutic (n)			
Corticosteroids	11	12	9
Tocolysis	0	2	3
Hospitalization	4	1	5
Birth			
Mean gestational age weeks	31±3	32±1	31±2
Cesarean (n)	11	12	9
Puerperium complications (n)	2	5	0

PPROM: preterm premature rupture of membranes; IUFD: intra uterine fetal death; TTTS: twin to twin transfusion syndrome; IUGR: intra uterine growth restriction; [†]2 triplet pregnancies with IUFD of 3 fetuses; *p<0.05; **p<0.001; χ^2 used for categorial variables; Kruskal-Wallis test for continuous variables

Table 2. Comparison on neonatal results of triplets over the three periods between 1996 and 2011

	1996–2000 n=12	2001–2006 n=12	2007–2011 n=9
NICU admission (n)	12	12	9
Fetus birthweight (gr)			
Fetus 1	1542±521	1563±303	1478±239
Fetus 2	1501±461	1540±302	1494±316
Fetus 3	1339±491	1524±292	1351±443
Neonatal mortality <28 days	1	0	0
Neonatal morbidity F1			
Respiratory	4	8	4
Infectious	3	3	3
Neurological	1	0	0
Neonatal morbidity F2			
Respiratory	3	8	6
Infectious	2	2	4
Neurological	1	0	0
Neonatal morbidity F3			
Respiratory	3	7	7
Infectious	3	2	4
Neurological	1	0	1

χ^2 used for categorial variables; Hest for continuous variables; no significant differences were found; all p>0.05

Discussion

The incidence of multiple gestations, particularly triplet and higher order pregnancies, has considerably increased over the past three decades, mainly due to the current widespread practice of ART, but also to the trend of delayed childbearing⁵. This increase is known to cause concern in contemporary obstetrical practice because these pregnancies are associated to poorer maternal and perinatal outcomes. The risk of adverse neonatal outcome undoubtedly increases with increasing number of fetuses, mainly as a result of preterm birth and/or low birth weight^{6,7}.

The introduction of ART had a significant impact in the incidence of multiple births worldwide. Nevertheless, the recent European Society of Human Reproduction and Embryology (ESHRE) report revealed that, for the first time in Europe since 1997, the proportion of three or more embryos transfers was reduced by 20% and the proportion of singleton embryo transfers was higher than that of triple embryo transfers. Overall, a remarkable reduction in triplet deliveries over the years is seen 3.6% in 1997 and 0.8% in 2009. The same was reported in studies from England and United States^{4,7}. These results give good expectations on better obstetric and neonatal outcomes related to collateral results of these widespread techniques.

In our results, the incidence of triplets remained relatively stable towards years. There was a significant trend toward a higher mean maternal age in the recent years, which may be related to the worldwide tendency of delayed childbearing and ART¹. There were no significant variations in the occurrence of obstetrical complications. Corticosteroids prescription and previous hospitalization rates did not suffer significant alterations through time. There was an increase in the antenatal use of tocolytic agents, but with no improvements could be seen in the mean gestational age at delivery, birthweight or the outcome of the newborns.

The remarkable progress in perinatal and neonatal care tocolysis, cerclage, ultrasound, hospitalization and bed rest, prenatal steroids, unfortunately, did not seem to have any noticeable effect on neonatal outcome in triplet gestations, which seems to stem primarily from prematurity and its inherent complications. Although intensive prenatal and neonatal care have a theoretical potential to improve perinatal outcomes on triplet pregnancies, there were practically no improvements reported in the outcome of triplets in the past three decades' data¹⁻³. In our

experience, as in other studies, neither prolongation of pregnancy nor improvements in morbidity or mortality in triplets could be documented.

Perinatal outcome in multiple gestations is also affected to a large degree by chorionicity². This is also valid for triplet pregnancies, as chorionicity has shown to influence mortality rates in triplets: MT triplet pregnancies have a significant higher risk of death 2.6-fold compared to TT triplet pregnancies^{2,8}. Besides a higher mortality risk, it is expected in triplets, as in twin pregnancies, a neurological disability risk related to chorionicity⁸. Therefore, monochorionic triplet gestations might have an equally or poorer prognosis than monochorionic twin gestations². On the other hand, chorionicity doesn't seem to have any influence on gestational age or birthweight at delivery¹. In our results, chorionicity contribute greatly to fetal death, since the cases registered occurred in monochorionic and dichorionic triamniotic triplets.

We recognize the small number of our sample as a limitation to the study, but even so, this confirms other authors in proving that triplets should be avoided due to their great risk of prematurity and neonatal morbidities. Consequently there is a significant increasing in medical costs on the health care system. Since most triplets are the result of ART, the focus should be maintained on limiting the number of embryos transferred during treatment protocols and, in an endless line action, on selective fetal reduction. Limiting the numbers of embryos transferred decrease the high order multiple pregnancy rates, without altering overall pregnancy rates and fetal reduction. Although far from an optimal solution to the problems associated with multifetal pregnancies, it seems to have fewer risks than those of continuing pregnancy with triplets and should be an option offered to these couples^{1,3,9-12}.

Triplets need high-quality antenatal care to optimize perinatal outcomes, which requires more monitoring. Early care focuses on determining chorionicity and screening for fetal complications, whereas later care concentrates on identifying and managing preterm birth, growth restriction, maternal complications, and planning for delivery^{13,14}.

Despite remarkable progresses in perinatal and neonatal cares, no noticeable impact in triplet gestation' outcomes was seen, sustaining that triplets should be avoided due to their great risk of prematurity and neonatal morbidities, either by limiting the numbers of embryos transferred or by fetal reduction.

References

1. Chibber R, Fouda M, Shishtawy W, Al-Dossary M, Al-Hijji J, Amen A, et al. Maternal and neonatal outcome in triplet, quadruplet and quintuplet gestations following ART: a 11-year study. *Arch Gynecol Obstet.* 2013;288(4):759-67.
2. Kawaguchi H, Ishii K, Yamamoto R, Hayashi S, Mitsuda N; Perinatal Research Network Group in Japan. Perinatal death of triplet pregnancies by chorionicity. *Am J Obstet Gynecol.* 2013;209(1):36.e1-7.
3. Weissman A, Ulanovsky I, Burke Y, Makhoul IR, Blazer S, Drugan A. Triplet pregnancies - a three-decade perspective: do we fare better? *Eur J Obstet Gynecol Reprod Biol.* 2013;170(1):82-4.
4. Ferraretti AP, Goossens V, Kupka M, Bhattacharya S, de Mouzon J, Castilla JA, et al.; European IVF-Monitoring (EIM) Consortium for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2009: results generated from European registers by ESHRE. *Hum Reprod.* 2013;28(9):2318-31.
5. ACOG Practice Bulletin No. 144: Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. *Obstet Gynecol.* 2014 May;123(5):1118-32.
6. Kulkarni AD, Jamieson DJ, Jones HW Jr, Kissin DM, Gallo MF, Macaluso M, et al. Fertility treatments and multiple births in the United States. *N Engl J Med.* 2013;369(23):2218-25.
7. Smith LK, Manktelow BN, Draper ES, Boyle EM, Johnson SJ, Field DJ. Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: population-based cohort study. *BMJ Open.* 2014;4(4):e004514.
8. Chaveeva P, Kosinski P, Puglia D, Poon LC, Nicolaides KH. Trichorionic and dichorionic triplet pregnancies at 10-14 weeks: outcome after embryo reduction compared to expectant management. *Fetal Diagn Ther.* 2013;34(4):199-205.
9. Wimalasundera RC. Selective reduction and termination of multiple pregnancies. *Semin Fetal Neonatal Med.* 2010;15(6):327-35.
10. Antsaklis A, Anastasakis E. Selective reduction in twins and multiple pregnancies. *J Perinat Med.* 2011;39(1):15-21.
11. Dodd JM, Crowther CA. Reduction of the number of fetuses for women with a multiple pregnancy. *Cochrane Database Syst Rev.* 2012;10:CD003932.
12. Drugan A, Ulanovsky I, Burke Y, Blazer S, Weissman A. Fetal reduction in triplet gestations: twins still fare better. *Isr Med Assoc J.* 2013;15(12):745-7.
13. Dafallah SE, Yousif EM. A comparative study of twin and triplet pregnancy. *Saudi Med J.* 2004;25(4):502-6.
14. Bricker L. Optimal antenatal care for twin and triplet pregnancy: the evidence base. *Best Pract Res Clin Obstet Gynaecol.* 2014;28(2):305-17.