



Management and Outcomes of 65 Quadruplet Pregnancies: Sixteen Years' Experience in France

J.C. Pons¹, L. Nekhlyudov², N. Dephot¹, S. Le Moal¹, E. Papiernik¹

¹Service de Gynécologie-Obstétrique, Maternité de Port-Royal, Paris, France; ²Mount Sinai School of Medicine, New York, NY

Abstract. Objective: data on the prognosis and management of multifetal pregnancies are of vital importance, particularly when the option of selective termination is considered. The present study details the obstetric management, neonatal outcome, and follow-up data of 65 quadruplet pregnancies in France.

Methods: to conduct the study, a questionnaire was sent to families registered with the National Association Helping Parents of Multiple Births (Association National d'Entraide des Parents de Naissance Multiples, A.N.E.P.N.M.).

Results: of 116 questionnaires sent to families of quadruplets born between 1972 and 1988, 65 were received. Of these pregnancies, 58 were obtained with ovulation induction agents, 2 with IVF (in vitro fertilization) and GIFT (gamete intrafallopian transfer) and 5 were spontaneous. Diagnosis was made prior to 13 weeks gestation in 87.2% of cases. Most mothers were hospitalized prior to delivery – mean duration of 47 days. The mean gestational age at delivery was 31.2 ± 3 weeks with a prematurity rate of 97%. Cesarean sections were performed in 51 cases and vaginal deliveries in 14. Neonatal and perinatal mortality rates were 68 and 104 per 1000, respectively. Birthweights of quadruplets ranged from 760 to 2455g with a mean of 1615 g.

Conclusion: management of quadruplet pregnancies in France consists of early diagnosis, echographical and clinical monitoring, early reduction of maternal activity and cesarean deliveries. Our management of such pregnancies is of high quality as reflected by our obstetrical results. Lack of adequate management, as perceived by families of quadruplets, exists at two levels: a psychological (lack of psychological support) and a financial (lack of specific help).

Key words: Quadruplet pregnancy, Multiple pregnancy, Multifetal pregnancy, Ovulation induction, In vitro Fertilization (IVF)

INTRODUCTION

The incidence of multifetal pregnancies has increased with the use of ovulation induction and assisted reproductive technologies. This increase in fetal number is accompanied by an increased risk for both the mother and infant. Multifetal pregnancy reduction is often an option in these cases; however, in order to justify its indication, one must consider maternal and fetal risks related to pregnancy reduction and those related to multifetal pregnancy in its absence.

At the present time, the actual prognosis of quadruplet pregnancies is not well known. International literature cites little about its evolution and management. Rates of spontaneous abortions and of embryonic losses are also unknown. A number of studies have been conducted in the area of quadruplet pregnancies. These include those by individual obstetrical services, providing information on the management of 23 quadruplet pregnancies, as well as two national studies; one English [2] with 41 cases and the other, a North American [3] with 71.

In our study, we present a national inquiry into quadruplet pregnancies in France. It was conducted in collaboration with the National Association Helping Parents of Multiple Births (Association National d'Entraide des Parents de Naissance Multiples (ANEPNM)).

MATERIALS AND METHODS

Data for this study was collected by a questionnaire sent to parents of multiple births. The questionnaire was designed to obtain information regarding maternal and paternal history; the couples' socioeconomic status; the origin of the pregnancy and its management; the delivery and the outcome of the infants. The questionnaire was relatively simple to complete by parents without access to medical records. Infants' health books were requested in the letter accompanying the questionnaire.

Questionnaires were sent by the ANEPMN to all families of quadruplets born between 1972 and 1988 registered with the association. The ANEPMN also received their completed forms; thus preserving the subjects' anonymity. PIGAS logic (INSERM 187) was used for data entry. Chi-square was used for statistical analysis.

RESULTS

A total of 116 questionnaires were sent to the families of quadruplets born between 1972 and 1988 registered with the ANEPMN, sixty five (56%) responses were received. This represents 31% of the 210 total quadruplet pregnancies recorded in France within these years [7].

Of the 65 mothers, 62 were French, two were North African and one North American. Their average age at the time of delivery was 28.5 years (range 25-41). Approximately one-third (35%) were laborers, 12.7% businesswomen, executives and self-employed, 4.8% farmers, 1.6% students and 24.4% unemployed. Past history of twins was found in 25 (38.5%) of the women; of those, 12 (48%) cases were in distant

relatives, 11 (44%) in close relatives and in 2 (8%) cases, the patients were themselves of twin pairs. The majority (57%) of the women were primigravidas, 19 (29%) had one child prior to the quadruplet pregnancy, 5 (7.7%) had two, 3 had three and one had four previous children. No significant past medical history was found in 54 (83.5%) of the women. Their socioeconomic status was middle in 36.9%, middle-higher in 46.2% and higher in 16.9%. None of them were of lower socioeconomic status.

Most of the fathers (95%) were European, one Asian and two of Maghrebine origin. Of the fathers, 45% were laborers, 26.5% middle managers, 21.9% executives and 6.3% farmers. No past history of twins was found in 73.3%. Two fathers were of twin pairs. Average paternal age was 31 years.

Only 5 (7.5%) pregnancies were spontaneous (of those, all women had past family history of multiple births). Most (89%) resulted from ovulation induction, either with clomid, clomid-hMG (human menopausal gonadotropin), hMG-hCG (human chorionic gonadotropin). Method of induction was unclear in 15 cases. Two pregnancies were achieved through IVF (in vitro fertilization) and GIFT (gamete intrafallopian transfer). A pregnancy reduction was unsuccessfully attempted in one case (all of these quadruplets were laser aborted at 23 weeks).

In most cases (82.7%), the quadruplet gestation was diagnosed by echography prior to the 13th week of gestation. All 65 pregnancies were followed regularly either by a general practitioner or an obstetrician, in a clinic or a hospital. The mean number of visits was 10.5 (range 2-50); the patient with 50 visits was followed in the clinic. Most (86.5%) were seen less than 16 times. Some patients (12.3%) were frequently visited at home, often weekly, by a midwife.

During the course of the pregnancies, 27 women indicated that they perceived the movements of each individual fetus.

Fifty-seven mothers (88%) were hospitalized at least once before delivery – of those, 37 (65%) with threatened premature delivery and 14 (24.6%) for systematic surveillance. One was hospitalized for pregnancy-induced hypertension and one with premature rupture of membranes. Average hospital stay was 47 days. The women were hospitalized either in the clinic (35%) or hospital (65%). During hospitalization, 48.2% were treated with beta-agonists, 14.3% beta-agonists/corticosteroids, 12.5% corticosteroids, 1.8% antihypertensives while 23.2% required only bedrest. Cerclage was performed in 28 (43%) of women although no significant difference was found in the length of gestation between those with cerclage (32.1 wks) and without (31.3 wks).

All women previously employed, except one, went on maternity leave. One patient continued to work as her quadruplet pregnancy (prior to 1975) was not diagnosed until several days prior to delivery. Most (84%) ceased work-related activity by the third month of pregnancy.

Average weight gain was 17.8 kg, ranging from one to 30 kg.

All but two patients delivered prematurely. Twenty-two delivered in private clinics and 43 in the hospital at the average of 31.2 weeks gestation (of 63 responses). Fourteen patients (21.5%) delivered vaginally (8 prior to 1980; 3 after 1988). While most (78.5%) delivered by cesarean section, only 14% of these (vs. half of vaginal deliveries) were performed earlier than 31 weeks gestation. Most women (80%) required general anesthesia, 5 (8.8%) epidural and 8 none.

After delivery, 34% of the patients reported pregnancy-related complications, includ-

ing severe anemia (22.7%), depression (18.2%), endometritis (18.2%) and abdominal hernias in two cases. No complications associated with betamimetics and/or corticosteroids were reported. The average post-partum hospital stay was 11.7 days (range 5–30 days).

Most (96.9%) newborn babies were premature (mean gestational age of 31.2 weeks). (Table 1). Eight infants (of whom one was stillborn) were born at term; other full-term infants had no health problems. Two patients delivered before 28 weeks gestation: one at 23 weeks, whose four infants died in utero and the other, at 26 weeks, whose infant died the day of delivery. Mortality rates are shown in Table 2.

Prenatal mortality (mortality of a fetus greater than 500g and 22 weeks gestation) was found to be 3.9% (39 per 1000). Early neonatal mortality was 6.8% (68 per 1000) – these 17 infants died of complications relating to prematurity. Four infants died before one year of age (one of septicemia on the 31st day and the others of sudden infant death (two at 5 months and one at 8 months) – a late neonatal mortality of 4.3 per 1000. The rate of sudden infant death in this series was 12 per 1000. Postnatal mortality (four of 232 alive after 28 days) was 1.8% (17.5 per 1000). Perinatal mortality was 10.4% (104 per 1000). Infant mortality comprised of 9% of 250 live borns (10 women lost one of their quadruplets, two lost half and two lost all four). Infant mortality rate varied as a function of birth order, with 63 per 1000 for the first-born of the quadruplet and 119 per 1000 for the last-born. As a whole, fetal-infantile mortality was 12.3%.

No difference was found with respect to birth weight and birth order. The infants in our population were, however, considerably smaller than average; at 32 and 33 weeks gestation, the 25th percentile of weight in our series corresponded to the 3rd percentile of the Leroy and Lefort curve. At 34 weeks, it fell below the 3rd percentile. (Tables 1 and 3).

Other characteristics of our quadruplets included a boy: girl ratio of 1.18, average height of 42cm, and Apgar scores of 7.72 at one minute and 9.1 at five minutes (Table 3).

Most of the infants (95%) were hospitalized, either in the neonatal intensive care unit or on regular pediatric units. The mean hospital stay was 51.2 days. With the exception of prematurity and hypotrophy, the majority of infants (66.8%) had no other clinical findings. Of those with medical complications, 43 (17.2%) presented with severe respiratory distress (RDS) secondary to hyaline membrane disease, 6 (2.4%) RDS and necrotizing enterocolitis, 3 (1.2%) necrotizing enterocolitis alone, 3 (1.2%) septicemia, 2 (0.8%) RDS and intraventricular hemorrhage, 1 (0.4%) intraventricular hemorrhage alone and 1 (0.4%) with persistent jaundice.

Most families suffered some socioeconomic consequences related to the birth of their quadruplets. The majority (73.3%) of the women who had been employed prior to their pregnancies did not resume their jobs; of those, 12 (36.5%) permanently quit, 18 (54.5%) had intentions to return to work at a later time and 3 (9%) were uncertain. More than half (54.5%) of the families had to relocate or enlarge their housing. The majority of the parents (87.3%) received household aide, the duration of which varied from 15 days to more than 2 years (34%). While only seven families received socio-professional benefits (relocation, change of working hours, etc.), 37 (60%) did not receive any additional financial assistance other than that granted per child by the French government.

Following their quadruplet pregnancies, 58 mothers (89%) had no additional children, 6 (9.5%) had one child and one (1.5%) had two more children.

Table 1 - Newborn characteristics as a function of gestational age

Gestational age	N. of women	N. of fetuses	Stillbirths	Deceased	Living	Birth weight (g) Q1	Birth weight (g) Q2	Birth weight (g) Q3	Birth weight (g) Q4
23	1	4	4	0	0	0	0	0	0
26	1	4	0	4	0	760	800	960	810
28	5	20	0	5	15	1856	1766	1346	1423
29	3	12	2	2	8	1535	1375	1475	1650
30	6	24	1	2	21	1456	1388	1316	1161
31	6	24	1	2	21	1483	1500	1458	1318
32	12	48	0	4	44	1444	1520	1485	1467
33	13	52	0	2	50	1746	1603	1611	1579
34	7	28	1	1	26	1802	1702	1647	1834
35	3	12	0	0	12	2033	2070	2086	1831
36	6	24	0	0	24	2116	2150	2228	1986
37	2	8	1	0	7	2455	1970	1835	1521
Unknown						4	4	4	6

Table 2 - Mortality rates of the quadruplets

Mortality	N. total infants	N. dead infants	Mortality rate (per 1,000)
Prenatal	260	10	38.5
Early neonatal	250	17	68
Late neonatal	233	1	4.3
Total neonatal	250	18	72
Perinatal	260	27	104
Infantile	250	22	88
Feto-infantile	260	32	123

Table 3 - Pregnancy outcomes: quadruplet characteristics

	Quadruplet 1	Quadruplet 2	Quadruplet 3	Quadruplet 4	Total
Live born infants	64	64	63	59	250
Weight at birth	1686 gm	1635 gm	1592 gm	1551 gm	1614 gm
Weight at 6 months	6271 gm	6079 gm	6100 gm	5952 gm	6105 gm
Apgar at 1 min	8.09	7.97	7.26	7.58	7.72
Apgar at 5 min	9.21	9.07	9.02	9.12	9.1
Neonatal Intensive Care					
Unit (%)	35.90	34.40	35.00	44	37
Hospitalization (%)	95.2	93.7	95	96.5	95
N. days in NICU	30.5	35.2	28.6	29.5	29.5
N. days in Pediatrics	43.1	44	45.9	48	45.5
N. days total	46.7	53.5	50.4	54.5	51.2
Non-respiratory disease	19	21	25	18	83
Severe respiratory disease	10	12	13	8	43
Living infants	60	58	58	52	228
Deceased infants	4	6	5	7	22
Still born	1	1	2	6	10

* Neonatal Intensive Care Unit.

No couples received any psychological counseling during the course of the pregnancies. Of the 64 who responded to this question, 18 indicated that they wished to receive some and would benefit from it. Family reactions were ascertained; and as a whole the parente claimed more anguish at the infants' arrival at home than at their birth. It was impossible to analyze further the psychological difficulties encountered by the families via our questionnaire.

DISCUSSION

According to the law of Hellin [10] established in 1895, the frequency of spontaneous twins is 1/89 births, that of triplets is 1/892 and that of quadruplets is 1/893, or approximately one of 700,000 births. In France, there is a clear increase in quadruplet pregnancies since 1976. Data published by INSEE in 1987 [7] cites a rate of one per 5.6 per million births in 1972 and 24.2 per million in 1986, a five-fold increase the rate of triplets tripled during this period). This increase in multifetal pregnancies may be accounted by the use of ovulation induction as is evident in our study as 58 (89%) of the pregnancies resulted from ovulation induction while only 5 were spontaneous.

In England, the number of quadruplet gestations has also increased with a rate of 1.23 per million prior to 1971 and 8.8 per million between 1982 and 1985, signifying a seven-fold increase [2]. In Japan, from 1968 to 1985, the rate of quadruplet pregnancies rose from one to 8 per million [6]. Quadruplet gestations have increased at a greater rate than that of triplets.

This increase in the frequency of quadruplet pregnancies is also reflected in their high incidence in specialized obstetrical hospital services, comprising a rate of 1:4734 [12] to 1:9377 [8].

As a whole, the frequency of high order pregnancies has become of extreme importance and a major public health concern. Further awareness of appropriate management and outcome of multifetal pregnancies is essential not only for adequate monitoring but also in the consideration of selective reduction of such pregnancies [7].

Several authors in the recent years have studied quadruplet pregnancies' management and outcomes. Following early diagnosis, maternal bed rest, while found by some not to increase gestational age, but improve neonatal outcome [8], is recommended by all. Early pregnancy diagnosis, essential to adequate management of quadruplets, was in fact achieved in most of our cases (87.2% were made prior to 13 weeks gestation). Additionally, in our study population, most women (84%) ceased work-related activity by the third month of pregnancy and 88% were hospitalized at least once before delivery with a mean hospitalization stay of 47 days. Other aspects of prenatal care including echographical monitoring [14, 16], tocolysis with betamimetics [1, 13, 16] and corticosteroids [8, 13, 14, 16] were of vital importance in the management of our French quadruplets. As the benefit to such dietary modification is unclear, hypercaloric and high-protein diets cited by others [13, 16], was not ascertained in our study.

Various complications are associated with vaginal deliveries of quadruplets including malposition, cord prolapse, and fetal collision [9]. Such complications require obstetrical interventions, such as version, extraction, and forceps, which may be traumatic for the hypotrophic, premature fetus [11] resulting from a multifetal gestation. Consequently, cesarean is cited as the preferable mode of delivery by most [5, 13-16], while natural delivery was noted in 5 observations [1, 9, 13]. The way of delivery was not specified in six cases [8]. In our study, cesarean sections were performed in most cases (78%) while vaginal deliveries accounted for only 22%. Authors of this study share in the opinion of others that an ideal delivery of quadruplets necessitates a cesarean section in the presence of an obstetrician, anesthesiologist, four neonatologists and four nurses/midwives [11, 15].

Maternal complications described by others included a case of premature rupture of membranes [16], anemia and shortness of breath [14] and two cases of preeclampsia [1,

9]. No maternal complications were cited by two authors [8, 13]. Our own results, based on larger data, revealed complications related to anemia, endometritis and hernias as well as depression.

Literature review, data analyzing gestational age and birth weight, are similar to ours, with the gestational age between 31 and 35 weeks and mean weight of 1249g [8], 1314g [12], 1422g [15] and 1950 [13].

Perinatal mortality was found between zero and 20% by most. The national British study [2], analyzing 41 quadruple pregnancies in England between 1975 and 1983 (at that time, its incidence was one in 138,620 births), revealed neonatal and perinatal mortalities of 207 and 220 per 1000, respectively (vs. 72 and 104 per 1000 in ours). In their study, 6.6% of their pregnancies resulted in liveborn infants, while 1.7% resulted in stillbirths. Prenatal mortality was found to be 30 per 1000 (less than the same study found for triplets).

Another national study, the largest to date-but-comparable in-size to ours, conducted by a group of researchers [3], analyzed 71 quadruple pregnancies followed between 1980 and 1989 in 27 American states and two Canadian provinces. Most of these pregnancies (94%), as 89% of ours, occurred secondary to ovulation induction. The mean duration of pregnancies was 31.4 weeks. The mean weight of infants at birth was 1482g. Cesarean was the preferred way of delivery (89%). Perinatal and early neonatal mortalities were relatively lower (6.7% and 3.7%, respectively) than in our study and elsewhere in literature.

Before concluding this inquiry, certain factors within this study require addressing. The study was conducted via a questionnaire that was designed to gather data relating to quadruplet pregnancies in France. Since the questionnaires were sent and received by the ANEPNM, the respondents' anonymity was preserved and thereby encouraged more complete and truthful responses. However, one may hypothesize that since only the ANEPNM members (approximately half of families with quadruplets born in France during the study years) were contacted, a selection bias may have been introduced. Those parents with more difficulties or those who lost all of their infants may not have joined this association or may have quitted. As a result, the reality of quadruplet pregnancy outcomes may be more somber than presented here.

The representation of professions and the socioeconomic status is comparable with that of the general population of France. Nevertheless, the lack of responses received from the lower socioeconomic class families may have constituted another selection bias.

Although this study may not be pronounced representative, it is of significant contribution to the area of quadruplet pregnancies. It is the only such carried out in France and attempts to gather cross-sectional data of quadruplets born in this country. It also constitutes one of the largest in the series of such studies published to this day and consequently provides much needed data on the management of multifetal pregnancies.

CONCLUSION

Worldwide and in our French study, the majority of multiple pregnancies are induced by ovulatory agents. Quadruplets resulting spontaneously or via IVF and GIFT are relatively few. On the contrary, ovulation induction is the origin of a real epidemic of quadruplet pregnancies.

As the duration of multifetal pregnancies is shortened as the number of fetuses is elevated, prematurity is the main prognosis of quadruplet pregnancies [9]. Prematurity is also the leading cause of morbidity and mortality of the quadruplets.

Obstetrical follow-up in France is of high quality consisting of early diagnosis, reduction in patients' activity, as well as clinical and echographical management. Our national obstetrical results are comparable with those of others.

The absence of appropriate management may lie in two areas: psychological – no patient in this study received such counseling, and financial – one can not ignore the economic difficulties that arise in the families of quadruplets.

REFERENCES

1. Bieniarz J, Shah N, Dmoski WP (1978): Premature labor treatment with ritodrine in multiple pregnancy with three or more fetuses. *Acta Obstet Gynecol Scand* 57: 25-30.
2. Botting BJ, MacDonald Davies I, Macfarlane AJ (1987): Recent trends in the incidence of multiple births and associated mortality. *Arch Dis Child* 62: 941-950.
3. Collins MS, Bleyl JA (1990): Seventy-one quadruplet pregnancies: management and outcome. *Am J Obstet Gynecol* 162: 1384-1392.
4. Evans MI, Fletcher JC, Zador IE, Newton BW, Quigg MH, Struyk CD (1988): Selective first trimester termination in octuplet and quadruplet pregnancies: clinical and ethical issues. *Obstet Gynecol* 71: 289-296.
5. Gonen R, Heyman E, Asztalos EV, Ohlsson A, Pitson LC, Shennan AT, Milligan JE (1990): The outcome of triplet, quadruplet, and quintuplet pregnancies managed in a perinatal unit: obstetric, neonatal, and follow-up data. *Am J Obstet Gynecol* 162: 454-459.
6. Imaizumi Y, Inouye E (1984): Multiple births rate in Japan, further analysis. *Acta Genet Med Gemellol* 33: 107-114.
7. La situation démographique en 1987. INSEE, n. 603 des Collections de l'INSEE, Série D, n. 131, Avril 1989.
8. Loucoloulos A, Jelewicz R (1982): Management of multifetal pregnancies: sixteen years' experience at the Sloane Hospital for women. *Am J Obstet Gynecol* 143: 902-905.
9. MacFee JG, LodEdward L, Jeffrey RL, O'Meara O, Josepher HJ, Butterfield LJ, Thompson HE (1974): Multiple gestations of high fetal number. *Obstet Gynecol* 44: 99-106.
10. Miettinen G (1954): On triplet and quadruplet in Finland. *Acta Paediatr* 43 (suppl. 99): 23-81.
11. Petrikovsky BM, Vintzileos AM (1989): Management and outcome of multiple pregnancy of high fetal order: Literature review. *Obstet Gynecol Survey* 44: 578-584.
12. Pons JC, Frydman R (1992): Les grossesses quadruples: prise en charge et evolution obstetrico-pédiatrique. *J Gynecol Obstet Biol Reprod* 21: 557-562.
13. Ron-El R, Caspi E., Schreyer P (1981): Triplet and quadruplet pregnancies and management. *Obstet Gynecol* 57: 458-463.
14. Shennan AT, Millican JE, Yeung PK (1979): Successful management of quadruplet pregnancy in a perinatal unit. *Can Med Assoc J* 121: 741-745.
15. Vervliet J, DeCleyne K, Renier M, Janssen P, Buyteart Ph, Gerris J, Delbeke L (1989): Management and outcome of 21 triplet and quadruplet pregnancies. *Eur J Obstet Gynecol Reprod Biol* 33: 61-69.
16. Wu IH, Kenneweg W, Langer A (1983): Successful management of a quadruplet pregnancy. A case report. *J Reprod Med* 28: 163.

Correspondence: Jean-Claude Pons, M.D. Service de Gynécologie-Obstétrique, Maternité de Port-Royal, 75679 Paris Cedex 14, France.