



Variable Outcome in Quintuplets Pregnancy Based on Obstetric Care

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The incidence of multiple pregnancies has increased dramatically over the last few years in developed countries, largely attributed to delayed childbearing and the increasing use of assisted reproduction technologies and ovulation inducing hormones. Relatively few countries have population-based statistics covering birth statistics. Of those that do, the numbers of quintuplet pregnancies rose sharply in the nineties while, at the same time, their delivery rates decreased greatly because of the use of fetal reduction. Fetal reduction is not possible or legal in some countries, Poland being one of them, and therefore obstetricians are faced with the challenges of quintuplet deliveries. Conservative treatment and management is difficult, and outcomes often vary greatly. Despite this, expert care provided at tertiary care centers can positively influence outcomes. The objective of this article is to present different care options and their consequences in two illustrative cases, as well as to establish a set of obstetric care and management goals that would allow prolongation of the gestation time. Quintuplet pregnancy is rare but poses relevant clinical problems to both the obstetrician and the neonatologist. It should be managed with close cooperation between all concerned. Due to the extreme and invariable risk of premature delivery associated with quintuplet pregnancies, we recommend early diagnosis, adequate prenatal care at one tertiary medical center, routine hospitalization and bed rest, repeated ante partum ultrasound surveillance with tests of fetal well-being, tocolytic therapy at first signs of the risk of premature labor, and specialized neonatology care after delivery.

Keywords: quintuplets, pregnancy

The incidence of multiple pregnancies has increased dramatically over the last few years in developed countries, largely attributed to delayed childbearing and the increasing use of assisted reproduction technologies and ovulation inducing hormones. In the United States, for example, over the past two decades the numbers of quadruplet and quintuplet pregnancies increased by 12-fold and 6-fold, respectively; these changes can be considered 'epidemic' considering the natural paucity of such pregnancies (Salihu et al., 2004). Relatively few countries have population-based statistics and, of those that do, the numbers of quintuplet pregnancies have raised sharply in the nineties while, at the same time, their delivery rates decreased greatly because of the use of fetal reduction.

Fetal reduction is not possible or legal in some countries, Poland being one of them, and therefore obstetricians are faced with challenges of quintuplet deliveries. Conservative treatment and management is

difficult, and outcomes often vary greatly. Despite this, expert care provided at tertiary centers care can positively influence outcomes. The objective of this article is to present different care options and their consequences as well as to establish a set of obstetric care and management goals which would allow to the prolongation of the gestation time. The following two cases are examples of different outcomes that were dependent on the care provided.

Two cases of quintuplet pregnancy were cared for and delivered at the Obstetric-Gynecologic Clinical Hospital of

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the Poznan University of Medical Sciences in Poland, within the year 2009. Both patients were diagnosed in the first trimester of pregnancy and treated as outpatients until gestation week 15 (patient A) and 17 (patient B). Patient A was treated by our department as an outpatient from the fifth week of gestation onward and offered prophylactic admission at 15 weeks. Patient B, on the other hand, was referred by an outside institution and transferred to our hospital at week 22 of gestation due to early uterine contractions. During both hospitalizations, the following standardized protocols were applied: bed rest, tocolysis with beta-mimetic agents (fenoterol) as needed, steroid therapy to enhance lung maturity, and thromboprophylaxis because of prolonged immobility. Ultrasonographic examinations and precision diagnostics using Doppler sonography (umbilical artery and middle cerebral artery) were performed every two weeks. Cervical length measurement was performed using transvaginal ultrasound if manual palpation showed cervical shortening or patient reported contractions. According to our antepartum multiple pregnancy protocol, no prophylactic cervical cerclage was used for prolongation of gestation in either case. During the hospitalizations, CTGs (cardiotocography) were performed two or three times daily, according to noticeable problems.

Vaginal smears were obtained on admission, following subsequent local treatment after verification of the causative organism. In both cases (A and B), induction of fetal lung maturation was commenced with 2 × 12 mg betamethasone (Celestan) injections within 24 h, as soon as there were signs of threatened premature labor and at the 24 weeks of gestation at the earliest. Patient A received two doses of betamethasone at 26 and 29 week of gestation due to increased frequency of uterine contractions which caused greater effacement and dilation of the cervix. Patient B received two doses of betamethasone at 24 week and 27 week of gestation due to regular uterine contractions.

Cesarean section was the planned mode of delivery for patients at more than 26 weeks of gestation. All decisions were arrived at with an experienced neonatology team and with parental agreement.

All infants were cared for by experienced neonatologists. The presence of respiratory distress syndrome (RDS) was diagnosed by an attending neonatologist and confirmed by a chest X-ray. Intraventricular hemorrhage was diagnosed by an experience physician ultrasonographic specialist.

Results

The age of the mothers was similar: 29 (patient A) and 28 (patient B) years, respectively. Patient A was multiparous, whereas patient B was nulliparous. Both pregnancies resulted after treatment with induction of ovulation by clomiphene citrate (CC; Table 1). Patient A was trying to get pregnant for a year and a half before pharmacological treatment with clomiphene citrate was indicated. The prescribed dose of CC was 50 milligrams per day for 5 days

starting on the fifth day of menstrual cycle, but only for the first month. In the following two months the dose was increased by 25 milligrams. The patient got pregnant after 3 months of treatment; however, she experienced ovarian hyperstimulation syndrome. Patient B was treated for primary infertility for 2 years and received clomiphene citrate for six menstrual cycles. The dose indicated was 50 milligrams, which was increased after 4 months to 100 milligrams. After 6 months of treatment a quintuplet pregnancy was confirmed; however, this patient was also diagnosed with ovarian hyperstimulation syndrome. Quintuplet A was treated at our clinic from the beginning of the pregnancy (5th week) and hospitalized at 15 weeks of pregnancy. In contrast, Quintuplet B was referred to our hospital by an outpatient clinic located in another town at 22 weeks of pregnancy when contractions had begun and the cervix was dilated to 3 cm. Patient B was then transported by ambulance for a distance of over 100 miles.

Quintuplet A was hospitalized at 15 weeks of pregnancy and was placed on prophylactic oral tocolytics using fenoterol due to silent effacement and dilation of the cervix to 1 cm; this was followed by intravenous (IV) infusions of the same medication at 20 weeks due to presence of persistent contractions. Quintuplets B were placed on IV infusions using fenoterol as soon as she was admitted to our hospital after the transfer ride of three hours duration. Quintuplets A were hospitalized for 120 days before delivery and Quintuplet B for only 5 days. Quintuplet A was delivered at 29 weeks of pregnancy by cesarean section, whereas Quintuplet B only managed to achieve a gestational length of 27 weeks before she too was delivered by cesarean section. In the case of Quintuplet B, the indication for cesarean section was spontaneous labor, which could not be managed with medication. The combined male:female ratio of the 10 infants was 4:6; and the birth weight ranged from 600 g to 1110g. Table 2 presents the parameters of all the quintuplets at birth.

After delivery, all neonates were treated by an experienced neonatology team in the Intensive Neonatal Care Unit. The respective gestational ages at delivery for

TABLE 1
Course of Pregnancy, Management and Delivery of the Quintuplet Pregnancies

	Patient A	Patient B
Maternal Age	29	28
GA at the time of hospitalization	15	22
Conception	Ovulation induction	Ovulation induction
Treatment during pregnancy	Prophylactic hospitalization Bed rest Fenoterol Steroids (x3)	Bed rest Fenoterol Steroids
GA at delivery	29	27
Mode of delivery	Cesarean section	Cesarean section

TABLE 2

Birth Parameters

	Quintuplets A	Quintuplets B
Birthweight and gender	1 1010g M	600g F
	2 1070g M	840g F
	3 1110g M	810g M
	4 760g F	710 g F
	5 870g F	670g F
Apgar at 1,5 minute	5,2	4
	4,5	6
	6,7	6
	8,8	6
	4,7	2
Arterial pH	7.31	7.31
	7.32	7.41
	7.33	7.26
	7.33	7.36
	7.31	7.32
Arterial Base Deficit	-2.2	-3.9
	-1.4	-4.3
	-2.8	-8.9
	-1.7	-6.9
	-2.8	-9.1

Quintuplets A were 29 weeks, and 27 weeks for Quintuplets B. Table 3 presents the neonatal outcome of all Quintuplets. All neonates were ventilated post delivery, either with infant flow or intermittent modulatory ventilation, but the time of ventilation was longer in Quintuplets B. The mean time of ventilation was 10 min for Quintuplets A versus 70 min for Quintuplets B. Respiratory distress syndrome occurred in all neonates, but the degree was more severe in Quintuplets B. Bronchopulmonary dysplasia was diagnosed in all of the Quintuplets B. Surfactant therapy was given to all the infants; however more doses were required for Quintuplets B. Retinopathy of prematurity was more severe in Quintuplets B as well. The hospital stay of the newborns in the intensive care unit was between 57 and 72 days for Quintuplets A, whereas Quintuplets B left the hospital after 121 days.

Discussion

Our hospital is a university referral institution for the entire North West of Poland. Its catchment area covers 40,000 square miles, and referrals normally come from as many as 32 local or regional hospitals and 350 outpatient and private clinics. The increase in induced higher order multiple pregnancies compelled us to establish a management plan for such pregnancies in 2010 upon which one could base clinical judgments.

After the mid-1980s, when the combination of IVF and ovulation induction therapies became recognized as the underlying causes of the 'epidemic' of multiple gestations, the literature proposed either managing quintuplet pregnancies conservatively or by offering the patient some form of fetal reduction (Stone & Berkowitz, 1995., Boulou et al.,

1993). Since the procedure of fetal reduction is not possible in every instance, and this being the case in our institution, conservative management becomes an important alternative to this radical approach. Because Quintuplet pregnancy carries an extremely high risk of premature delivery, with a concomitant increase in prenatal mortality and morbidity, it is obvious that, when using conservative treatment, the ultimate outcome relates primary to gestational age at delivery (Stone & Berkowitz, 1995).

Before moving on to the management plan it is worth to mention that infertility is usually a very complex and difficult problem to treat. It is very important that the treatment of infertility is managed by gynecologists with specialized training and experience in this area. Both of the Quintuplets were treated by gynecologists without sufficient experience in the treatment of infertility, this could have been the cause of ovarian hyperstimulation and in consequence quintuplet pregnancy.

The ultimate as well as the ideal goal of any management plan for quintuplet pregnancy is the prolongation of the gestation time as much as possible, thus allowing the medical team to deliver the fetuses safely and to have expert neonatal care available. Because all of these requirements can best be fulfilled by tertiary prenatal centers, quintuplet pregnancies should be managed at such facilities from the beginning of pregnancy (preferably one center through the whole pregnancy). In the cases described above, Quintuplets A were under our care from the beginning of pregnancy as outpatients and inpatients and regular uterine contractions occurred much later in the pregnancy compared to Quintuplets B. This latter case arrived at our hospital with regular uterine contractions and cervical dilation, only after having experienced a transfer by ambulance of long duration. Early transfer (shortly after the diagnosis had been made) to a tertiary center would have removed the need for patient transport between cities after labor had commenced as well the stress associated with these logistic movements. Both circumstances were completely avoidable and could possibly have an impacted negatively and significantly on the early contractions. Studies which have investigated the outcomes of triplet pregnancies monitored as inpatient or outpatients have shown that the group monitored as inpatients had outcomes of a higher gestational age and birth weight and less fetal growth retardation (Adams et al., 1998; Skrablin et al., 2002). There is no reason to think that such findings would not apply to quintuplets as well.

Routine hospitalization and bed rest are not new interventions, but they remain controversial among obstetricians (Crowther & Han, 2010; Komaromy & Lampe, 1977; Lazar et al., 1984; Loucopoulus & Jewelewicz, 1982). The argument for prolonged hospital stay is based on the delay of the onset of labor, better placental blood flow, relief of discomfort and the availability of immediate medical treatment when necessary (Kraemer et al., 2009). Although several studies have

reported that bed rest is not beneficial in terms of neonatal outcome in twins and triplets (Lazar et al., 1984), others have observed that it may prolong the pregnancy, reduce prematurity and prenatal mortality as well as reduce such complications as hypertensive disorders and influence the incidence of intra-uterine growth restriction (Ron-El et al., 1992). Here again, there is no reason to believe that these arguments would not apply to quintuplets as well.

As pregnancy duration is greatly decreased in quintuplet gestations, bed rest logically should be initiated early. In fact, there is no reason to delay it because the negative effects of standing, prolonged standing and work on the onset of contractions is well described in the literature (Henriksen et al., 2005; Teitelman et al., 1990). In our opinion, the best management plan includes outpatient visits at 2-week intervals up to 14 weeks of pregnancy, followed by prophylactic hospitalization from the early second trimester of pregnancy until delivery.

The importance of a written protocol for early diagnosis and management plan cannot be overstated. Ultrasound antepartum surveillance is the mainstay for monitoring fetal wellbeing and is essential for early diagnosis; vaginal ultrasound reveals the number of gestational sacs with accuracy (Ayres & Johnson, 2005). Ultrasound assessment of fetal growth and amniotic fluid volume should be scheduled every two weeks including nonstress tests and biophysical profiles later into the pregnancy and Doppler velocimetry in case of complications such as hypertension or fetal hypotrophy (Gregic et al., 2009).

Changes in cervical lengths changes may indicate a risk for preterm birth. Pelvic examination by the same care provider or transvaginal ultrasound measurement of cervical effacement and dilation is thus important to determine the risk of premature labor. Although such data is not available for quintuplets, other studies have shown that a cervical length of 25 mm in the 23rd week has a premature delivery risk of 50% before 33 weeks of gestation for a triplet pregnancy (To et al., 2000). A cervix length of less than 25 mm from the 15th up to the 20th week of pregnancy is associated with a premature delivery risk of 100% before 28 weeks gestation (Welsh & Nicolaidis, 2002). In case of Quintuplets A, the cervical length was determined every 2 weeks or when the patient reported contractions. On the other hand, Quintuplets B arrived in the hospital with regular contractions and dilation, which required more frequent examinations.

The literature does not show significant benefits from cervical cerclage placement in the midtrimester in a pregnancy complicated with a short cervix in terms of reduction of preterm births. The benefit of prophylactic cerclage without the presence of cervical insufficiency in triplet pregnancy is not clearly proven (Bernasko et al., 2006), and gestation is not invariably prolonged by cervical cerclage. Routine cerclage in triplet pregnancies has been recommended by some authors (Dew, 1978; Dommergues et al.,

1995; Itzkowic, 1979); however, in these studies the duration of gestational age of those who had cerclage was slightly less than those who had none (Kraemer et al., 2009). There is no literature on prophylactic cerclage in quintuplets and it was not considered for our cases.

Prophylactic parenteral tocolytic therapy is generally not used by our center, but with persistent contractions and/or silent effacement or dilation of the cervix, parenteral therapy with beta-mimetic agents was initiated. Quintuplet A received oral tocolytics from 16 week of pregnancy because of persistent contractions and was switched to intravenous infusions at 22 week of gestation. Quintuplets B were treated with intravenous tocolytics as soon as she arrived in our hospital; however, in this instance we diagnosed regular contractions and cervical dilation as well.

Our center offers prophylactic corticosteroid administration to all women expected to deliver between 28 and 34 week of gestation. Both Quintuplet A and B received corticosteroids for lung maturity and a greater chance of better neonatal outcome despite of the fact that Quintuplets B delivered at 27 weeks of gestation.

In our center, cesarean section is the preferred route of delivery in cases of higher order multiple pregnancies, the indication being the expected prematurity and the fact that proper assistance is easier to provide in planned deliveries during normal working hours. Several studies have reported increased prenatal morbidity, in particular low Apgar scores, asphyxia and respiratory complications, among vaginally delivered triplets (Barkehall-Thomas et al., 2004; Ho et al., 1996; Lipitz et al., 1989), whereas such complications are rarely observed in series where cesarean delivery is the norm (Albrecht & Tomich, 1996; Barkehall-Thomas et al., 2004; Kaufman et al., 1998). We think that in the case of quintuplets the mode of delivery should not be debated, and it should always be a cesarean section to increase the probability of neonatal survival and optimum management of neonatal problems. Quintuplet A and B were respectively delivered by cesarean section prematurely because of persistent contractions and progressing dilation.

Not unexpectedly, and as indicated by the results presented in Table 3, the neonatal outcome was strongly associated with gestational age of the quintuplets at delivery. The two week difference in delivery time between Quintuplet A and B was associated with greater severity of complications for Quintuplet B. Quintuplets B, delivered at 27 week of pregnancy, required prolong assisted ventilation due to severe respiratory distress syndrome compared to Quintuplets A and also required more doses of surfactant to improve their lung function. These neonates were also diagnosed with severe degree of retinopathy and were hospitalized for almost twice as long as Quintuplets A. This outcome difference clearly indicates that in quintuplets every single day of prolonged gestation is important and counts in

TABLE 3

Neonatal Outcome

	Ventilation/ time	IVH	RDS	Surfactant	BPD	ROP	Paraenteral feeding	Days of hospitalization
Quintuplets A								
I	IF	No	I	0	0	1	2	72
II	IMV	No	III	1	0	2	4	57
III	IMV	II/III	III	2	0	0	12	57
IV	IF	No	0	0	0	2	3	72
V	IMV	No	III	1	0	2	5	62
Quintuplets B								
I	IMV	II	IV	2	1	3+	20	121
II	IMV	I	IV	1	1	3+	15	121
III	IMV	I	IV	2	1	3+	61	121
IV	IMV	0	IV	1	1	3+	11	121
V	IMV	0	IV	2	1	3+	24	121

Note: IF — infant flow; IMV — intermittent modulatory ventilation; IVH — intraventricular hemorrhage; RDS — retinopathy of prematurity; BPD — Bronchopulmonary dysplasia.

TABLE 4

Antepartum Management of Quintuplet Gestation

Controlled use of ovulation induction drugs as well as other assisted reproduction technologies	Experienced obstetrician.
Early diagnosis (first trimester)	Early diagnosis of any multiple pregnancy is crucial for the best management and neonatal outcome.
Tertiary care hospital	The patient should be referred to tertiary care hospital as early as multiple pregnancies are diagnosed. Preferably the patient should be under the care of one clinic.
Routine hospitalization/bed rest	Visits at 2-week intervals up to 14 week of pregnancy and then prophylactic hospitalization from the early second trimester of pregnancy until delivery. Bed rest should be initiated early during pregnancy.
Ultrasound antepartum surveillance	Ultrasound antepartum surveillance is the mainstay of monitoring the fetal wellbeing and is essential for early diagnosis.
Cervical length measurements	Pelvic examination or transvaginal ultrasound measurement of cervical effacement and dilation is very important to determine the risk of premature labor.
Tocolytic therapy	Prophylactic parenteral tocolytic therapy is generally not used, but with persistent contractions and/or silent effacement or dilation of the cervix, parenteral therapy with beta-mimetic should be initiated.

obtaining better neonatal outcome and improving neonatal morbidity and mortality.

The literature on the natural history of pregnancies containing four or more fetuses is sparse (Skrabin et al., 2000) and individual reports of quintuplet gestations are not common. Many recent reports are associated with multifetal pregnancy reduction which, in our opinion, is far from the optimal solution of for reducing complications associated with multiple pregnancies. Besides reducing the number of preterm deliveries, it poses a real threat of losing the entire pregnancy. With reduction, loss rates as high as 16% of triplet (Boulot et al., 1993; Evans et al., 1995; Lipitz et al., 1989; Skrabin et al., 2000) and 20% of higher order gestations (Evans et al., 1995; Skrabin et al., 2000) are reported. Having said this, however, it is also important to note that the conservative management of

higher order pregnancies is not well described in the literature, and likely that the optimal clinical management of higher order pregnancies is not yet resolved (Evans et al., 1995; Stone & Berkowitz, 1995).

Quintuplet pregnancy is rare but it poses relevant clinical problem to both the obstetrician and the neonatologist; it should be managed with close cooperation between all concerned. Conservative management of this type of pregnancies is possible (Table 4). Due to extreme risk of premature delivery associated with quintuplet pregnancies, we recommend early diagnosis, adequate prenatal care by one tertiary medical center, routine hospitalization and bed rest, ultrasound antepartum surveillance with tests of fetal wellbeing, tocolytic therapy at first signs of the risk of premature labor and specialized neonatology care after delivery.

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