Chapter 8

Quadruplets and Quintuplets

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Abstract

A high-order pregnancy is always a challenge not only for the couple but also for the obstetrician, the pediatricians, the midwives, and the whole stuff of an obstetric clinic. The breakthroughs of infertility treatments have made more couples to postpone the birth of their children until they feel professionally and financially safe, many times after the age of 40. The advanced age of the mother puts extra pressure to the clinician for immediate success, leading to a rise of high-order pregnancies until the introduction of regulations and laws in many countries. The cost of a quadruplet and quintuplet pregnancy can be unbearable, not only financially but also psychologically. The management of such a pregnancy is also challenging since its beginning and to the end. Modern techniques and methods can also be difficult to be implemented on a quadruplet of quintuplet pregnancy because of the fear of losing four or five embryos at once. At the same time, the limited number of cases makes it almost impossible for studies to be made and guidelines to be established for most of the cases.

Keywords: quadruplet, quintuplet, high-order, management

1. Introduction

"High-order pregnancy" is defined by the presence of three or more fetuses. Before the introduction and widespread of modern fertility methods, a high-order pregnancy was rare and unique. The first recording of quadruplets, the Smiths, was in 1750 [1]. In 2009, Samson described again the Gehri quadruplets, born in 1880, the first to have survived to adulthood.

In 1896, the Lyon quintuplets died within 15 days from birth while the Dionne quintuplets born in 1934 were the first to survive through infancy [2]. Nowadays, even with the galloping improvement in perinatal care, a high-order pregnancy still represents a challenge where outcome is not always favorable.

Dionys Hellin still since 1895 was trying to predict the occurrence of multiples in nature [3]. The "Hellin-Zeleny's rule" (after the publication of Zeleny's work in 1921 [4]) was a simple way to predict the occurrence of multiple births. Among others, Peller in 1946 [5] and Allen in 1960 [6] proposed new versions or improvements of this rule with various imitations [7, 8]. The incidence of multiple births has changed over time, presenting a decline until the late 1970s and an increase thereafter [9]. It is estimated that in the United States in 1980 there were 37 triplets or higher order births per 100,000 births, rising up to 1935 per 100,000 births in 1998 [10, 11]. Quadruplet and quintuplet or higher births raised from 229 and 40 in 1989 to 627 and 79, respectively, in 1998. Since 1999, a decline is observed, and in 2016, there were 1014 per 100,000 triplets or higher order births, 217 quadruplet and 31 quintuplet and other higher order births [12]. In France, the increase of triplets or high-order pregnancies reached 310% and in England and Wales 430% [13]. There is a difficulty to estimate accurately how many of these high-order pregnancies are a result of natural conception, estimates put this number around 20% [14].

Modern fertility treatments are the most important reason for the increase in multifetal pregnancies. Medical societies around the world have recognized the problem and have published guidelines in order to minimize the frequency of high-order pregnancies resulting from fertility treatment. The economic side of the matter is also of great importance. In 1996, there was a report concluding that the cost per woman who delivered singletons or twins was approximately $39,000, while the cost per woman who delivered triplets or quadruplets was up to $340,000 [15]. In 2006, the annual cost of each preterm neonate in the USA was estimated around $51,600 [16]. Since 90% of high-order pregnancies are born prematurely, considering that the average gestational age at delivery for quadruplets is 29.5 weeks and for quintuplets 29 weeks [17], it is easy to understand the impact of multifetal pregnancies to a tight health system budget. Aside the financial cost to the health system, a high-order pregnancy can wreck any family financial planning. The average costs per child is about $233,680 in the USA (for a child born in 2015, data published by the U.S. Department of Agriculture), without the college education. The birth of four, five, or more children can make the cost for the family unbearable.

Together with the progress in infertility treatment, a lot of progress is made in prenatal and neonatal care. Ultrasound has changed maternity care with the early diagnosis of fetal conditions. New techniques, such as fetal reduction, have made possible a favorable outcome from a pregnancy with normally poor outcome. Nevertheless, a high-order pregnancy still remains a challenge for both the clinician and the mother, not only during pregnancy but also after birth.

2. Pathophysiology of high-order pregnancy

A multiple gestation can either occur by a single fertilized ovum splitting (monozygotic), or by the fertilization of more than one ova at the same time (multizygotic), or even by the

combination of the above. For monozygotic pregnancies, the timing of the fertilized ovum splitting dictates the pregnancy chorionicity. When the splitting occurs soon after the fertilization, it results in a diamniotic-dichorionic pregnancy. A diamniotic-monochorionic pregnancy occurs when the fertilized egg splits between the third and the eighth day after fertilization and a monoamniotic-monochorionic when the splitting occurs between the ninth and twelfth day. Conjoined twins are formed when the twinning process occurs after the formation of the yolk sac. A high-order pregnancy can harbor any of the above listed combinations [18]. Fetuses that result from the splitting of the same fertilized ovum are called monozygotic and the babies have the same genetic profile, physical characteristics, and sex, while fetuses that result from the fertilization of more eggs have different genetic background and can be of different sex.

A multiple pregnancy can occur as a consequence of a single ovum fertilization. Liu in 2010 [19] reported a case of a monozygotic quadruplet pregnancy as a result of IVF, although the pregnancy ended in the ninth week of gestation due to chromosomal abnormalities. Nnadi in 2013 [20] described a case of monozygotic quadruplet pregnancy conceived naturally that ended in an elective cesarean section of a set of monochorionic tetra-amniotic quadruplets at 37 weeks of gestation. Neubecker in 1962 [21] and Rau in 1940 [22] reported two cases of monozygotic quintuplet pregnancies, indicating the possibility of a quadruplet and quintuplet pregnancy arising from a single ovum.

The term superfecundation is used to denote the fertilization of a second or more ova within hours or days after a first fertilization, which can result in a multiple pregnancy. The two fertilizations can be either due to differed sexual intercourses or as a consequence to sexual intercourse in a context of in vitro fertilization and embryo transfer. Peigné in 2011 [23] reported a case of a multiple pregnancy as a result of intercourse 1 day after the oocyte pick-up, while Milki in 2001 [24] reported a case of multifetal pregnancy occurring after sexual intercourse 5 days prior to oocyte retrieval. Superfecundation raises the issue of paternity among separately fertilized ova. Wenk et al. in 1992 [25] reviewed a parentage test database of 39,000 records of parents involved in paternity suits and reported the percentage of heteropaternal superfecundation among dizygotic twins to be as high as 2.4%. In contrast to superfecundation, the term superfetation is used to describe a multiple pregnancy resulting after ovulation, and fertilization occurs during an established pregnancy. Superfetation has not yet been proven possible in humans, although it exists in animals [26].

3. Predisposing factors for a high-order pregnancy

There have been described several factors related to increased incidence of multiple pregnancy, in particular twin pregnancy. Factors predisposing to a multiple pregnancy differ between monozygotic and multizygotic pregnancies in nature. The difficulty to determine any predisposing factors for quadruplet and higher order pregnancies lies in the limited series of patients and the lack of available data. Therefore, many factors associated with twin pregnancies are also considered to have a possible influence on the incidence of high-order pregnancies.

Before the introduction of modern infertility treatments, the prevalence of monozygotic twinning was relatively constant among different origins, oscillating between 3 and 5 per 1000 live births [27]. On the other hand, the prevalence of dizygotic twinning differs concerning race, maternal age, and family history of twinning. Black women have the highest rate of dizygotic twins followed by Asian women and finally white women. Moreover, women with a family history for dizygotic twinning, such as a previous dizygotic pregnancy or being part of or related to a set of dizygotic twins, have greater probability to conceive dizygotic twins compared to women with no family history [14].

Since the early 1970s, maternal age was considered an important factor that could influence the conception of a multiple pregnancy, with a reported fourfold increase of dizygotic twinning rate between the ages of 15 and 37 [28]. Maternal age does not seem to affect monozygotic multiple pregnancy rates, as shown in multiple studies [29]. Women between the ages of 35 and 41 are more likely to have a multiple gestation. The increment in multifetal pregnancies is probably related to higher basal FSH levels for women over the age of 35 compared to younger women. Higher levels of FSH can be associated with the maturation of multiple follicles in natural cycles and consequently the occurrence of a multiple pregnancy [30].

There is evidence that a woman's somatometric parameters are associated with a multiple pregnancy. Women with a BMI over 30 are more likely to conceive more than one babies compared to women with normal BMI [31–34]. Noteworthy, a higher BMI increases the probability of multizygotic pregnancies but not monozygotic ones. Women's height has been associated with multiple pregnancies, even though its impact is less important than weight [34]. Women who are taller than 173 cm seem to have higher probability for dizygotic twinning compared to women shorter than 165 cm [31, 33].

Some lifestyle choices have also been proposed as predisposing factors for multiple pregnancy. Multivitamins and folic acid supplementation have been associated with an increased incidence of multiple gestation, even though the results were not statistically significant [35]. In order to confirm that the use of folic acid increases the rates of multiple pregnancies (up to 40%), more trials have to be performed [36]. Coffee consumption, smoking, and alcohol have also been evaluated for their possible positive correlation with multiple pregnancy without fertility treatments [37]. This observation is surprising, since smoking and alcohol are known to have negative effects on the fetus and the pregnancy outcome. Kapidaki in 1995 [38] showed that for each cup of coffee per day there was an increase in the odds for multifetal pregnancy. Parazzini in 1996 [37], on the other hand, found no relation between multiple pregnancy and the extent of coffee drinking. In the same study, however, they found that women who were drinking ≥15 alcohol units per week and those who were smoking ≥10 cigarettes per day were more likely to conceive a multifetal pregnancy. In any case, more studies are necessary in order to have results that are more reliable.

The use of contraceptive pill and the time after its discontinuation are associated with multiple pregnancy. The theory behind this affirmation is an increase in the secretion of gonadotropins shortly after the cessation of the pill that could result in multiple pregnancies. Many studies, since the 1970s [39–42], have denoted an increase in twin pregnancies after the cessation of oral contraceptive pills. A study by Campbell in 1987 [43], however, found no statistical

significance between the cessation of oral contraceptives and the incidence of monozygotic or dizygotic twinning. In the same study, no significance was found between the time after cessation of contraceptives and the occurrence of twin pregnancy. As far as high-order pregnancies are concerned, there are no available data due to the limited number of cases.

Wen et al. in a study in 2004 [44] observed that women with high-order pregnancies were tended to be white (78.8% for twins, 89.4% for triplets, and 94.8% for quadruplets and more) and older (67.6% of mothers of triplets, 64.6% of quadruplets, and 46.3% of twins were older than 30 years). Moreover, they were more likely to be married (72% for twins, 90.6% for triplets, and 97.4% for quadruplets and more) and of higher education. Mothers of triplets, quadruplets, and more were less likely to have smoked during pregnancy and more likely to have received prenatal care earlier (93.6 and 94.6% for triplets and quadruplets in first trimester compared to the 85.4% for twin pregnancies). Finally, they were more likely to be women undergoing their first pregnancy (34.1% for twins, 51.2% for triplets, and 52.7% for quadruplets and higher). In a study by Luke and Brown in 2008 [45], which included the U.S. births from 1995 to 2000, the same demographic characteristics are evident among mothers of quadruplets, white, older women of higher education and at lower parity, married, and non-smokers.

Nowadays, the most important predisposing factor for multiple pregnancy is modern fertility techniques. Induction of ovulation, the transfer of more than one embryos, IVF, ICSI, assisted hatching, or even the culture media have all been associated with increased incidence of a multiple gestation [14]. Some of the above have been strongly associated with multiple pregnancy, and regulations have been established in many countries either by law or official guidelines in order to reduce the incidence and any eventual complications of a multiple pregnancy (for instance, there is a limitation of the number of embryos allowed to be transferred). Many studies exist in literature, including case reports, for quadruplet/quintuplet pregnancies after single/double blastocyst transfer. Quadruplet pregnancies have been reported after the transfer of only one [46] or two embryos [47–49], with variable chorionicity. There are also case reports of quintuplets originated from one fertilized egg (the Dionne quintuplets) and two [50, 51] or three blastocysts [52].

4. Diagnosis of a multifetal pregnancy

Early diagnosis of a multiple pregnancy is crucial for achieving the best outcome and for preventing as many complications as possible, either maternal or fetal [53]. The preferred method to diagnose a multifetal gestation is by ultrasonography. This method is accurate enough to reveal a multiple pregnancy by the fourth week of gestation, although the number of yolk or gestational sacs can be misleading as early in pregnancy [54].

The term "vanishing fetus" or "natural fetal reduction" is used to describe the loss, through miscarriage, of one or more fetuses during a multiple gestation. This phenomenon can be observed up to the 16th week of pregnancy, and it can be either asymptomatic or it can present with bleeding, pain, or abdominal cramps. Before the introduction of ultrasound, a vanishing fetus could only be diagnosed after delivery [55]. Dickey et al. estimated that the prevalence of a vanishing

fetus before the 12th week of a quadruplet pregnancy could be as high as 65% with great variability among different researchers [56]. They also showed that the probability of a spontaneous absorption in a multiple pregnancy was directly related to the initial number of gestational sacs and to maternal age ($p < 0.001$ and $p < 0.01$, respectively). In the same study, they concluded that the average duration of reduced twin pregnancies with initially four sacs was 11 days shorter when compared to the duration of unreduced twin pregnancies (254 days–243 days, $p < 0.001$). In addition, the birth weight of naturally reduced twins was lower compared to the weight of unreduced twins (2024 ± 668 g compared to 2453 ± 575 gr, $p < 0.003$).

Ultrasonography plays an important role in the diagnosis of chorionicity and placentation of a pregnancy. Determining chorionicity is crucial, since twin and triplet pregnancies with at least one monochorionic pair have greater perinatal morbidity and mortality [57, 58]. Perinatal mortality in quadruplets tends to be five times higher when a monochorionic set is present compared to quadra-chorionic [57]. Adeghite et al. in 2007 [59] compared the differences in neonatal complications between quadra-chorionic quadramniotic and trichorionic newborns. There was statistically significant higher incidence for almost all complications considered within the trichorionic group. This group also had statistically significant higher rates in neonatal death when compared to the quadra-chorionic group. Furthermore, trichorionic infants were born much earlier and weighed less compared to the quadra-chorionic ones: 28 vs. 32 weeks and 69% <1000 g vs. 13% <1000 g ($p < 0.001$), respectively. There was no difference between the groups in regard to the mode of delivery. Some data suggest that the use of modern infertility treatment methods is associated with monozygotic twinning, although the data for some of these methods are conflicting [60]. Since 75% of monozygotic twins are also monochorionic [61], women who have undergone such treatments and have a multifetal gestation must be suspected for monochorionicity. Chow et al. in 2001 in a study of 464 multiple gestations showed that in multiple gestations arising from artificial reproduction treatments, there is a correlation between the number of fetuses and the rates of monochorionic pairs [62]. Monochorionic pairs were present in only 2.1% of twin pregnancies, while in quadruplet and quintuplet pregnancies the rates were as high as 25% ($p < 0.05$). Chow et al. finally confirmed the observation made in earlier studies that a monochorionic pair is more likely to be found in a naturally conceived gestation.

Early ultrasound evaluation can identify placentation correctly in over 90% of multiple gestations, and in case this is not possible, the gestation should be treated as monochorionic [17]. The data regarding the incidence of placenta previa in a multiple gestation are conflicting. Some of them suggest that placenta previa is up to 40% more common in twin pregnancies [63], probably due to limited space in the endometrial cavity [64], whereas others argue that the incidence of placenta previa is not correlated with the number of embryos [65].

5. Complications and management of quadruplet/quintuplet pregnancies

Women with quadruplets and higher-order pregnancies are at increased risk for obstetric complications compared to women with twin pregnancies. Moreover, a dose-response

relationship can be found for certain complications of the pregnancy. Wen et al. [44] in 2004 compared the outcomes in women with twins, triplets, quadruplets, and high-order pregnancies from 1995 to 1997. They concluded that women with triplets and more were in greater risk for pregnancy associated hypertension, eclampsia, anemia, diabetes mellitus, placental abruption, premature rupture of the membranes, and cesarean delivery, even after the adjustment for important confounding factors. Wen also compared the maternal health outcomes. Women with triplets, quadruplets, and higher order are predisposed to develop pregnancy-associated hypertension and diabetes mellitus (7.68% for twins, 10.32% for triplets, and 11.57% for quadruplets and higher order for hypertension, while for diabetes mellitus the rates were 3.34% for twins, 5.97% for triplets, and 6.75% for quadruplets and higher order). Twins were less frequently delivered by cesarean section (51.21% compared to 86.78 and 84.87% for triplets and quadruplets or higher, respectively) and had less chances for a premature rupture of the membranes (6.66% for twins, 11.17% for triplets, and 10.65 for quadruplets and more). The rise in rates for cesarean delivery as the number of fetuses increases could also explain the low rates of induction of labor and use of forceps and vacuum among triplets and quadruplets compared to twin pregnancies. The study by Luke and Brown in 2008 [45] also came to the same results that quadruplet pregnancies have greater chances for pregnancy-associated complications when compared to twin pregnancies. In the study by Luke and Brown, the p-value was <0.0001 for diabetes mellitus, incompetent cervix, induction of labor, stimulation of labor, tocolysis, cesarean delivery, premature rupture of the membranes, infant death of ≥ 1 baby, birth at ≤ 29 weeks of pregnancy, and <0.05 for pregnancy-associated hypertension and eclampsia.

Multiple pregnancies present increased spontaneous loss rates, and these rates increase in parallel with the increase of the number of the fetuses. The authors estimate that a quadruplet pregnancy has a 25% chance for a spontaneous loss, while a quintuplet has three times more, up to 75%. This rise is more obvious when these rates are compared with the ones for a twin and a triplet pregnancy (8 and 15 respectively) [66].

Preterm labor has been proven the most common maternal complication in high-order pregnancies [67], and it is directly associated with the increased perinatal morbidity and mortality observed in these pregnancies, while the rates of pregnancy complications seem to be raised alongside the increase of the number of fetuses [14]. More than 90% of high-order pregnancies are born prematurely, with the approximate gestational age at delivery for quadruplets to be estimated around 29.5 weeks, while for quintuplets this point is up to 29 weeks of gestation [17]. In USA, in 2016, the 93% of quadruplets (217 cases) and the 100% of quintuplets and higher order pregnancies (31 cases) have been born before the 34th week of gestation [12].

In order to prolong the pregnancy, several methods have been used. Bed rest, either hospitalization or home rest, is a method still widely used. Although some researchers considered bed rest the most important mode of treatment and it was used to be advised to all patients [53], Crowther in 2001 [68] for a Cochrane review synthesized seven controlled trials including twin and triplet gestations. Bed rest has been proven ineffective to reduce preterm labor, while on the same time it was psychologically distressing.

Another method widely used for reduction of preterm labor in high-order pregnancies was prophylactic cervical cerclage. In the 1970s, it was suggested that prophylactic cervical cerclage could be beneficial in the prevention of preterm labor for multiple pregnancies [69]. More than 40 years after that, prophylactic placement of cervical cerclage—transabdominal or transvaginal—is considered of undetermined value [70] or of no significance regardless of the indication [71]. Straus in 2002 compared a group of quadruplet and quintuplet pregnancies with cerclage and one without and found that the birth weight was higher in the cerclage group ($p < 0.001$). Despite the higher birth weight in the cerclage group, it was also evident that the perinatal morbidity and mortality were higher (69 vs. 32% for the non-cerclage group for morbidity and 10.26 vs. 5.55% for mortality), although the results due to the small number of cases were of no statistical significance. Strauss concluded that in order to see if prophylactic placement of cervical cerclage has anything to offer to multiple pregnancies, randomized controlled studies have to be made, something difficult due to the limited number of multiple pregnancies.

Tocolysis is also another method for the prevention or delay of preterm labor. Several researchers and clinicians used several different medicines, as prophylactic treatment. Prophylactic tocolysis is not recommended since the data show no effect on risk reduction for preterm birth and further studies are needed [72]. Prolonged use of these medicines is also not recommended since tocolysis does not seem to have a significant result to extend the pregnancy for more than 7 days [73].

Cervical pessary is another widely used strategy to prevent preterm labor. Research has been made for singleton and twin pregnancies, with conflicting results [74]. For multiple pregnancies, Liem et al. [75] in a randomized controlled trial, cervical pessaries were not effective in preventing preterm birth, but showed some success for cases with a cervical length of less than the 25th percentile, but further research is needed with more patients. The researchers also noted the low cost of a pessary and the fact that it was well tolerated by the women in the trial, making it a choice to consider in developing countries.

Another strategy used to prolong a multiple pregnancy is the use of progesterone, with vaginal distribution to be preferred than the intramuscular one in terms of fewer maternal side effects [76]. Although for singleton pregnancies, progesterone is considered an effective choice, for multiple pregnancies there is insufficient evidence for the recommendation of its use, with or without a short cervical length, despite the use of 17-alpha-hydroxy-progesteronecaproate by some experts in women with multiple pregnancy and prior spontaneous preterm birth [77].

It is estimated that about 25–30% of preterm labor is the result of preterm premature rupture of the membranes [78]. Luke and Brown in 2008 [65] published a study in which they compared risk rates for maternal and neonatal complications among high-order pregnancies. According to their results, quadruplet pregnancies are more likely to be diagnosed with preterm premature rupture of the membranes (10.64% compared to 9.61% for triplets and 6.17% for twin pregnancies, $p < 0.001$). In another retrospective cohort study of more than 290,000 live births, premature rupture of the membranes complicated 19.6% for quadruplet and 100% for higher order (>4) pregnancies compared to 19.3% for triplets, 11.2% for twins,

and 3.1% for singletons [79]. In the same study, the proportion of preterm birth attributable to premature rupture of the membranes for extremely preterm gestational ages (before 28 weeks of pregnancy) was 50% for quadruplets and 100% for higher order pregnancies compared to 26.9, 34.6, and 26.5% for triplets, twins, and singletons, respectively ($p < 0.001$). On the other hand, premature rupture of the membranes for late preterm gestational ages (34–37 weeks of gestation) contributed to 10% of quadruplets, 12.2% of triplets, 11% of twins, 10.2% of singletons, while no high-order pregnancies could reach that gestational age ($p < 0.001$). Finally, for quadruplets and high-order pregnancies, Caucasian race was a common aggravating factor, and premature rupture of the membranes in multifetal gestations increased with gestational plurality and occurred at earlier gestational age.

Hypertensive disorders of pregnancy are more common among multiple pregnancies, in particular quadruplet pregnancies have a reported incidence of pregnancy-associated hypertension up to 40% with earlier and more severe onset [80]. Day in 2005 [81] showed that the rate of mild and severe preeclampsia is similar for triplets and quadruplets, with the exclusion of women who delivered before 28 weeks. The rates for development of any pregnancy-associated hypertensive disorder were 19.6% for quadruplets, 20% for triplet pregnancies, 12.7% for twins, and 6.5% for singleton pregnancies. The same study showed that the rates for severe pregnancy-associated hypertensive disorders were 1.1, 3.1, 1.6, and 0.5% for quadruplet, triplet, twin, and singleton pregnancies, respectively. When comparing quadruplet with singleton pregnancies, quadruplets were strongly associated with severe pregnancy hypertension disorders ($p < 0.01$). The studies by Wen in 2004 [64] and Luke and Brown in 2008 [65] also showed that women with quadruplets are more likely to develop pregnancy-associated hypertension compared to twins. Since placenta plays an important role in preeclampsia [82], the increased mass of the placenta in multifetal pregnancies is probably associated with the occurrence of preeclampsia. Preeclampsia is often atypical, with hypertension not always present, but with abnormal laboratory values. Hardardottir in 1996 [83] reported that in a series of three cases delivered for preeclampsia among eight quadruplet pregnancies, only one developed hypertension, none proteinuria, one had edema, and two had elevated uric acid >5 mg/dl. In the same study, the mean age for women with quadruplets and preeclampsia was 34 years and without preeclampsia was 28.6 years, with no statistical significance. Despite the progress in understanding the pathogenesis of preeclampsia, little progress has been made in terms of treatment [84].

Molar pregnancy coexisting with live fetuses is a rare condition, with cases resulting to the delivery of a live fetus to be even scarcer. There are reports of quadruplet pregnancies with coexisting mole with different management and outcomes. The outcome does not usually include viable fetuses [85]. No guidelines for the management of a multiple pregnancy coexisting with a complete hydatidiform mole and live fetuses occur. Therapeutic abortion is always an option to consider, since the chances for delivering a live fetus are very low and the maternal risks are very high [86]. Tariq in 2014 [87] published a case report of a molar pregnancy diagnosed at 22 weeks where continuation of the pregnancy with close surveillance was decided. The mother was under close monitoring and went into preterm labor at 33 weeks. Three viable fetuses were delivered.

Gestational diabetes can be expected to be more common among women with multifetal pregnancy. It has been shown that women with twins have higher rate of gestational diabetes than women with singleton pregnancies [88] and women with triplets tend to have higher rates than twins [89]. Wen in 2004 [64] showed a direct relationship between the number of fetuses and the rates of gestational diabetes. Luke and Brown [65] in 2008 confirmed these results by comparing twin and quadruplet pregnancies (p-value < 0.0001). The rarity of quadruplet and quintuplet pregnancies makes further research necessary in order to confirm that the rise in gestational diabetes rates continues among quadruplet and quintuplet pregnancies.

Women carrying multiples are at increased risk for urinary tract infection, with the rates for multiple pregnancies to be up to 4.6% compared to 3.7% for singleton pregnancies [90], possibly because of the larger size of the uterus or the levels of progesterone in the maternal circulation.

Nutrition and weight gain are of great importance in a multifetal pregnancy. Unfortunately, there are no recommendations available for quadruplet and quintuplet pregnancies. What is expected, is that weight gain might be faster than with triplets and twins, and although there are recommendations for singletons, twins and triplets, that has not yet been possible for higher-order pregnancies [91]. Multivitamin supplements such as folic acid, calcium, and vitamins are recommended, due to the high nutrient needs of the mother and the fetuses. Anemia and iron deficiency are the most common pregnancy-related complications [92, 93] and are associated with a series of maternal and neonatal complications, such as preterm delivery [94], low birth weight [95], birth asphyxia [92], and iron deficiency in high-risk infants [96]. Anemia and iron deficiency are more prevalent among women with a multifetal pregnancy compared to women carrying singletons, so nutriments and supplements containing iron are highly recommended [93]. Vitamin D and calcium through supplements, essential fatty acids through fresh or canned oil-rich fish, and additional energy and macronutrients are advised but there no studies estimating the exact daily requirements [91].

The positive effect of corticosteroid administration in singleton pregnancies is well established. In multifetal gestations however, the datas are still limited. There have been reports suggesting that betamethasone administration in quadruplet births is associated with increased uterine contractions, preterm labor with cervical change, and preterm labor requiring tocolysis [97]. Despite that, a single course of corticosteroids is recommended for all multifetal pregnant women at risk of preterm delivery between 24 and 0/7 weeks and 33 and 6/7 weeks of gestation. In addition, a single repeat dose should be administered to women less than 34 weeks of gestation, at risk of preterm delivery within 7 days, and whose prior dose of corticosteroids was administered more than 14 days before [98].

Quadruplets and quintuplets have higher neonatal and perinatal mortality compared to triplets. Skrablin et al. in 2000 [99] published a study of 51 quadruplet and quintuplet pregnancies compared to 156 triplet pregnancies. They found no significant difference when compared the two groups for stillborns and neonatal mortality ≥28 weeks. On the other hand, they observed a statistically significant difference when they compared neonatal deaths ($p = 0.02$), the "Discharged Alive" (76.3% for triplets, 54.9% for quadruplets and quintuplets, $p = 0.003$), early neonatal mortality for ≥1000 g ($p = 0.04$), and perinatal mortality for >24 and ≥28 weeks of pregnancy (both $p = 0.005$). Mortality and morbidity seem to be related with preterm delivery,

and high-order infants have comparable rates compared to singletons and twins of the same gestational age [70, 100]. In a retrospective study by Hernandez in 2009 [101], 26% of multiple pregnancies had at least one death (including triplets). In particular, 54% of quadruplet and 100% of quintuplet pregnancies had at least one death, while the average weight at birth was 750 g for dead quadruplets and 1341 g for surviving quadruplets ($p < 0.0007$). Chibber in 2003 [102] in a study including 100 triplet, 27 quadruplets, and 10 quintuplet pregnancies showed that low birth weight is crucial for perinatal mortality and morbidity, with low birth weight complicating most of the 34 neonatal deaths in the quadruplet and quintuplet groups. Multiples are at increased risk of growth problems compared to singletons, with the degree of intrauterine growth restriction to increase as the number of fetuses increase. In the USA, in 2016, 77.1% of quadruplets were below 1500 g and 96.2% below 2500 g. When considering quintuplets and more, these rates rise up to 80.7 and 100%, respectively. The limited space in uterus and the limited nutrient supply might be responsible for low birth weight [103]. Unfortunately, there are no specific data for quadruplets and quintuplets.

A low Apgar score at birth is a common concern for neonatologists when a high-order pregnancy ends. Chibber in 2003 [102] highlighted the differences between triplet and higher pregnancies when the Apgar scores of the first and fifth minute were compared. The mean first-minute Apgar score for triplets was 7.8, while for quadruplets and quintuplets was only 6.2 ($p < 0.01$). When compared the five-minute Apgar score, this was 8.8 for triplets and 7.2 for quadruplets and quintuplets ($p < 0.05$). Skrablin et al. in 2000 [99] also observed statistical significances in their study, with the mean first-minute Apgar score for triplets to be 6.4 and for quadruplets-quintuplets 4.9 ($p = 0.003$) and the five-minute Apgar score to be 7.6 for triplets and 6 for quadruplets and quintuplets ($p = 0.01$).

There are also some rare complications which have been reported in high-order pregnancies, but due to the limited number of cases, no guidelines are available. Fetofetal transfusion has been reported in quadruplet pregnancies [104–106] as well as quadruplet pregnancies with conjoined twins [107, 108]. Another complication that has been described in a quadruplet pregnancy was the rupture of an unscarred uterus, raising the debate of the ideal delivery time for a high-order pregnancy [109]. High-order pregnancies have significant higher rates of peripartum hysterectomy compared to singleton pregnancies [110], although the data from quadruplet and quintuplet pregnancies are limited.

6. Multifetal pregnancy reduction

High-order pregnancies hold a significant risk of miscarriage as well as neonatal and maternal morbidity and mortality. Fetal reduction, since its introduction in 1988 by Evans and his associates [111], has shown encouraging results in regard to the outcome of a multiple pregnancy [66]. Antsaklis et al. in 2004 [112] in a series of 313 multiple pregnancies showed that fetal reduction can reduce the risk of pregnancy loss and severe prematurity in quadruplets and higher order pregnancies and result, in most cases, in at least one live neonate. In particular, he compared the two largest groups, that is triplets and quadruplets reduced to twins, as for miscarriage (8.25 vs. 8.96%), preterm delivery defined as <33 weeks (11.18 vs. 19.67%), and total fetal loss rate (15.41 vs. 14.93%). Altogether, the reduction of a high-order pregnancy

with more than four fetuses to twins holds the best outcome. When the median gestational age at delivery was compared, this was higher for >4 fetuses reduced to twins rather than triplets (36 vs. 31 weeks respectively) and for quadruplets reduced to singletons rather than twins (38 vs. 36 weeks respectively). Evans in 2014 [66] showed a 25% decrement of fetal loss when quadruplet pregnancies were reduced to either twins or singletons. In the same line, when quintuplets were reduced to twins, the risk of fetal loss was decreased by 50%.

Fetal reduction can be done either transabdominally or transvaginally. When the transabdominal approach is used, the proposed time frame is between the 10th and 16th week of gestation, although the optimal timing is often arbitrary (Davis in 2014 [113] cited four different time frames suggested by four different researchers). Fetal reduction using the transvaginal approach can be performed earlier in the pregnancy when the placenta and the embryo are smaller. There is some skepticism concerning the transvaginal approach and the possibility of introducing vaginal bacteria [114]. Therefore, each center follows the practice they are more experienced in, since it has been shown to affect significantly pregnancy outcomes in terms of fetal loss and prematurity. Evans et al. in 2001 [115] studied the evolution of pregnancy outcomes across time: before 1991, from 1991 to 1994, and after 1994. Loss rates decreased from 13.2 to 9.7 to 6.4%, respectively. More specifically, loss rates for quadruplets reduced to twins were 13% before 1994 and only 6.6% thereafter, although it is difficult to identify whether experience, better ultrasonography techniques, or both played the most important role.

Fetal reduction is usually done by directly injecting KCL as a cardiotoxic agent, although aspiration of the embryonic parts has also been used [116]. Another reduction method used is thermocoagulation [117], either bipolar cord coagulation or radiofrequency ablation with similar results [118, 119]. Ligation of the cord as well as suture and compression of the cord on the uterine wall have also been used for fetal reduction [120].

First trimester reduction is a relatively simple and safe procedure with good results [121]. Nevertheless, many authors propose to perform fetal reduction in the second trimester after prenatal screening and possible detection of fetal abnormalities. Geva et al. in 2000 [122] published a series of 38 multifetal reduction procedures in the second trimester compared to 70 fetal reduction procedures in the first trimester. He included four quadruplet gestations in the first group and 18 in the second. The mean gestational age for quadruplets reduced to twins in the second trimester was higher compared to quadruplets reduced to twins in the first trimester (36.7 ± 1.2 vs. 33.6 ± 3.9 weeks respectively, $p = 0.01$). Accordingly, the mean birth weight of quadruplets reduced to twins in the second trimester was higher compared to the mean birth weight of quadruplets reduced to twins in the first trimester (2111 ± 3089 g vs. 1762 ± 503 g respectively) (statistically significant). When all pregnancy complications were compared, no statistically significant difference was found between the two groups, except for premature labor ($p = 0.046$). The authors concluded that when the second trimester is chosen for reduction, detection of fetal abnormalities and selection of an affected fetus can improve the outcome to similar results as for a first trimester reduction. This observation motivated several authors to propose the 15th–16th week of pregnancy as the optimal moment for fetal reduction [113].

Fetal reduction has shown to be a valuable option for high-order pregnancies (≥4) [123, 124]. Antsaklis et al. in 1999 [125] compared the outcomes of reduced twins (from quadruplets and triplets) to unreduced twins. There was no difference in regard to perinatal or

obstetric complications. When he compared the outcomes of reduced twins between the 10th and 11th week of gestation from triplet or quadruplet pregnancies, there were still no significant differences between the two groups. Wang in 2007 [126] studied 37 multifetal pregnancies reduced between the 12th + 1 and 25th week of gestation. He concluded that the incidence of preeclampsia is decreased after reduction. Boulot in 1993 [124], from a series of 61 multifetal pregnancies, concluded that the rate of miscarriage is lower when the aim of the reduction is twins rather than singletons. However, he found that the miscarriage rate was significantly lower when one fetus was reduced compared to 2 fetuses (6 vs. 24% respectively, $p < 0.05$). In another study by Timor-Tritsch in 2004 [127], the total pregnancy loss (at less than 24 weeks) for reduced quadruplets was at 1.8% (2.4% for the transabdominal route and 0% for the transvaginal route, $p = 0.56$). In the same study, the total pregnancy loss (at less than 24 weeks) for reduced quintuplets was at 14.3% (15.4% for the transabdominal route and 12.5% for the transvaginal route, $p = 0.65$). Multiple studies have concluded that the birth weight, gestational age at delivery, and perinatal mortality rate were directly correlated with the final number of fetuses [112, 128, 129]. Reductions of more than one fetus can be done in one session; however, when 5 or more fetuses need to be reduced to a singleton, two sessions seem to have better results than one, with 1 week interval between the sessions [66].

Another point to consider when counseling a couple about fetal reduction is the possibility of one of the remaining fetuses to develop intrauterine growth restriction. There is evidence that fetal reduction is not associated with an increased risk of intrauterine growth restriction, unless it is performed on a high-order pregnancy [130]. Depp et al. in 1996 [131] have shown that when quadruplet and higher order pregnancies were reduced to twins the incidence of one or more IUGR among fetuses was greater compared to non-reduced twins. The frequency of discordance was directly linked to the pre-reduction fetal number. The frequency in the non-reduced twin cohort was at 16.3%, and the rate of discordance for quadruplets reduced to twins was at 26.1%,while for higher order reductions reduced to twins was at 34.2%.

When discussing with a couple about the risks of multifetal pregnancy and the option for fetal reduction, the psychological strain needs to be addressed and properly managed. The first reaction of a couple when a multiple pregnancy is diagnosed is generally favorable, although parents need to be counseled about the risks of a multifetal pregnancy. A proposed fetal reduction can cause anxiety to the couple, but eventually the majority of patients accept to abort some fetuses in order to preserve the lives of the others [132]. Specifically, when quadruplets or more fetuses are involved, couples are more inclined to go through a reduction procedure [133], and in some cases, they consider reduction as mandatory [121], although ethical issues may always be a concern.

7. Delivery of a quadruplet or quintuplet pregnancy

The delivery of high-order pregnancies is challenging for the mother, the obstetricians, and pediatricians. Malpresentations are common, while the babies often require intensive care and special treatment, considering that more than 90% of high-order pregnancies are born

prematurely. Average gestational age at delivery is estimated around 29.5 weeks for quadruplets and 29 weeks for quintuplets [17], although term delivery has also been reported, mostly as case reports [20, 134, 135]. The rates of preterm birth in the USA at <37 weeks of gestation are estimated at 96.77% for quadruplets and 100% for quintuplets and more. When it comes at <34 weeks, the estimated rates are at 93.09% for quadruplets and 100% for quintuplets [12].

Cord prolapse, hemorrhage, and abruption of the placenta are undesirable possible complications for any vaginal delivery, but in a high-order pregnancy where the mother and the fetuses are more vulnerable are even more undesirable. While there are many reviews about the mode of delivery for twin and triplet gestations, this is not possible for quadruplet and quintuplet pregnancies. For quadruplet pregnancies, vaginal delivery has been reported [136]. Cesarean section is preferred if the obstetrician is not confident enough with vaginal delivery maneuvers [137], while on the same time when an elective cesarean is selected, it allows the optimal preparation and logistic conditions [138]. The time of the elective delivery is also to be considered, with Elliot reporting choosing the 34 + 0 weeks for quadruplets [17]. Finally, further research is needed in order to safely determine whether cesarean or vaginal delivery can affect the Apgar score of the newborns [139].

The most challenging cases of quadruplet and quintuplet pregnancies are the cases where preterm labor of at least one fetus has occurred and delayed interval delivery is considered an option in order to improve the chances of survival for the remaining fetuses. Such cases with at least one newborn surviving have been published, both for quadruplet [140, 141] and for quintuplet pregnancies [142]. For twin and triplet gestations, some authors consider delayed internal delivery a viable option [143, 144], while for quadruplet and quintuplet pregnancies, there are still not enough data.

8. Conclusion

In cases of a quadruplet, quintuplet, or any high-order pregnancy, early diagnosis is crucial for the further management and treatment. The international literature concerning pregnancies with more than three fetuses is still limited, and it is not going to be any better in the future. The prevalence of high-order pregnancies after the rise until 1996 is tending to normalize, making—again—unique and rare such cases. The lack of cases and the diversity of these cases make it difficult to manage the complications, which will probably arise during a high-order pregnancy. New treatments used for singleton or twin pregnancy complications cannot always be considered as options for treating a high-order pregnancy, especially when no data are available. Beside the scientific interest for these cases and the challenge they pose to anyone dealing with them, it is always important to remember that the couple suffers the greater burden. The psychology of the couple should never be underestimated. Even by the beginning of the pregnancy, the possibility of a result not favorable is always in mind, so additional support is necessary. Fetal reduction is a method that improves the outcome of these pregnancies and could be offered as an option when there is experience with the procedure and no other limitations are present (e.g. religious).

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