

# Monozygotic pregnancies conceived by in vitro fertilization: understanding their prognosis

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**Objective:** To analyze the outcomes and particular characteristics of monozygotic (MZ) pregnancies conceived by in vitro fertilization (IVF).

**Design:** Retrospective data analysis.

**Setting:** Large private-academic fertility center.

**Patient(s):** IVF-conceived MZ pregnancies.

**Intervention(s):** Statistical analysis of MZ pregnancy outcomes depending on fetal order and pregnancy reductions status.

**Main Outcome Measure(s):** Spontaneous pregnancy reduction, pregnancy loss, take-home baby rate, perinatal mortality, gestational age at delivery, and birth weight.

**Result(s):** A total of 72 of 3,426 pregnancies (2.1%) were MZ, and 70 were included in the study. Of these, 34 cases (48.5%) were high-order multiple pregnancies (HOMP), and 36 (51.5%) were non-HOMP. In the HOMP group, only 2.9% (1 of 34) had a complete pregnancy loss while 38.8% (14 of 36) of the non-HOMP were lost by 20 weeks' gestation. Of the HOMP patients, 73.1% therapeutically reduced the MZ component, and a statistically significant difference in gestational age of delivery ( $37.8 \pm 3.2$  vs.  $28.1 \pm 7.7$ ) and birth weight ( $2796 \pm 865.8$  vs.  $1110.0 \pm 731.6$ ) was seen when compared with nonreduced HOMP.

**Conclusion(s):** Twinning with MZ is encountered in a small but important number of pregnancies derived from assisted reproduction. The prognosis for these patients is unfavorable, particularly for single-implantation MZ pregnancies and for nonreduced HOMP. Patients who do not spontaneously reduce a MZ-HOMP by 12 weeks may benefit from therapeutically reducing the MZ component of the pregnancy. (Fertil Steril® 2011;95:606–10. ©2011 by American Society for Reproductive Medicine.)

**Key Words:** ART, high-order multiple pregnancy, IVF, monozygotic, multifetal pregnancy reduction, pregnancy outcome

Twinning is not a rare condition in humans. Although the incidence varies among different populations around the world (6 in 1,000 in Asia; 10 to 20 in 1,000 in the United States; and 40 in 1,000 in Africa), it is now estimated that 1 in 40 newborns will be part of a twin pregnancy (1). The higher incidence of multiple pregnancies secondary to in vitro fertilization (IVF) is well recognized, and approximately 32% of IVF pregnancies are twin or higher order conceptions (2). This higher incidence is a consequence of the intrauterine replacement of multiple embryos, which often results in the implantation of more than one zygote (e.g., dizygotic twinning). Since the first report of an IVF monozygotic (MZ) twin pregnancy in 1984 by Yovich et al. (3), it has been suggested that not only is the incidence of dizygotic pregnancies increased after IVF, but that splitting of the zygote is also more prevalent. In a recent meta-analysis, Vitthala et al. (4) reported that the risk of MZ pregnancy after assisted reproductive technology (ART) is 2.25 times greater when compared with natural conception.

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Monozygotic pregnancies are at an increased risk of adverse outcomes when compared with singleton and dichorionic twin pregnancies (5). Higher incidences of premature delivery (6), growth discordance (7), developmental anomalies (8), and mortality rates (6) have been well documented in naturally conceived MZ pregnancies. Monozygotic pregnancies conceived by ART create a different context: the higher incidence of multiple pregnancies in IVF increases the risk of having a MZ pregnancy as part of a high-order multiple pregnancy (HOMP). Furthermore, IVF gestations themselves may have an increased risk of low birth weight, preterm delivery, placental abruption, preeclampsia, and perinatal mortality, as reviewed by Kalra and Molinaro (9) in 2008.

To date, publications regarding ART-conceived MZ pregnancies have focused mainly on determining the incidence and etiology (mechanical, biochemical, or epigenetic) of this phenomenon (4, 10). To our knowledge, ours is the first large study to assess the reproductive outcome of IVF MZ pregnancies in a comprehensive fashion. We examined the outcome of these pregnancies to more fully and properly counsel patients facing this particular situation.

## MATERIALS AND METHODS

The IVF database of a large private-academic fertility center was reviewed for all clinical pregnancies (e.g., at least one gestational sac recorded on early ultrasound) occurring between June 1, 2002, and June 30, 2008. Pregnancies achieved by the use of autologous and heterologous

oocytes in both fresh and cryopreserved-thawed embryo transfers were included. A MZ pregnancy was identified when more than one fetal pole with cardiac activity was seen and recorded in a single gestational sac or when the number of fetal poles with cardiac activity recorded was greater than the number of embryos transferred during routine early ultrasonographic examination. A HOMP was identified based on the documentation of more than two fetal poles with cardiac activity, regardless of the number of sacs identified. A complete pregnancy loss was defined as the absence of viability in any fetus at 20 weeks' gestation; a partial pregnancy reduction was defined as the loss of viability in at least one fetus with the survival of at least one sibling.

As per our routine office protocol, the first vaginal ultrasonographic examination is performed 7 days after the doubling of  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) concentration has been confirmed (usually 23 days after oocyte retrieval). During this assessment, the number, size, and localization of gestational sacs are documented. A second ultrasonographic evaluation is performed a week later in which the number, size, and characteristics of gestational sacs, yolk sacs, fetal poles, and fetal cardiac activity are recorded. Chorionicity and amnionicity are also determined at that visit (11). The ultrasound examination is repeated on a weekly basis until patients are discharged to their obstetric provider in gestational weeks 7 to 9. All HOMP are referred to a maternal-fetal medicine specialist for counseling regarding carrying the pregnancy or electing to undergo multifetal pregnancy reduction (MPR).

Pregnancy outcomes were obtained directly from patients via mail or telephone. Perinatal mortality, pregnancy loss, pregnancy self-reduction, number of newborns per delivery, gender of newborns, gestational age at delivery, and birth weights were recorded. Details from MPR were obtained directly from the maternal-fetal medicine specialist performing the procedure. Pathologic confirmation of amnionicity, chorionicity, and placental vascular anomalies was unavailable because many patients underwent delivery outside our institution. All patients signed consent forms for retrospective review their records for research purposes, and institutional review board approval was obtained to undertake this retrospective study.

Pregnancy outcomes (e.g., partial and complete pregnancy losses, number of newborns per delivery, gestational age at delivery, birth weight, perinatal deaths, and take-home baby rate) were analyzed by comparing patients who had a MZ pregnancy as part of a HOMP with those who had a single-implantation MZ pregnancy. To perform a risk/benefit analysis of self-reduction and elective fetal reduction, the outcomes of HOMP pregnancies were evaluated by reduction type and status. Statistical analysis was performed by chi-square and analysis of variance (ANOVA), where appropriate.  $P < .05$  was considered statistically significant.

## RESULTS

A total of 3,801 clinical pregnancies were diagnosed during the study period, and fetal cardiac activity was identified in 3,475 (91.4%) after ultrasonographic examination. Overall, 72 MZ pregnancies were identified, reflecting an incidence of 1.89% (72 out of 3,801) of clinical pregnancies or 2.07% (72 out of 3,475) of pregnancies with fetal cardiac activity. Obstetric information was unavailable from two patients, so we could fully analyze only 70 MZ pregnancies for this study.

The mean ( $\pm$  standard deviation) patient age was  $36.5 \pm 5.5$  years, with an average oocyte age of  $32.3 \pm 5.5$  years. Donor oocytes were used by 22.8% (16 out of 70) of these MZ pregnancies, and cryopreserved embryos were transferred in 11.4% of these cases. An average of  $2.5 \pm 0.7$  embryos were transferred per cycle. The details of the ovarian stimulation protocol, oocyte insemination procedure, and embryo transfer are presented in Table 1.

A HOMP with at least three fetal poles with cardiac activity was identified in 34 of the MZ cases (48.5%); the other 36 (51.5%) pregnancies originated from the split of a single-implanted zygote (non-HOMP) (Fig. 1). In the HOMP group, 25 (73.5%) were triplets, eight were quadruplets (23.5%), and one was a quintuplet.

**TABLE 1**

**Patient and cycle characteristics.**

Patient age (y)	36.5 $\pm$ 5.51
Oocyte age (y)	32.34 $\pm$ 5.55
Cycle type	
Autologous fresh	47 (67.10)
Autologous cryo	7 (10)
Heterologous fresh	15 (21.40)
Heterologous cryo	1 (1.40)
Ovarian stimulation type <sup>a</sup>	
GnRH antagonist	14 (20.28)
Down-regulation	46 (66.66)
Microflare	9 (13.04)
Oocyte insemination type	
Conventional	42 (60)
ICSI	28 (40)
Transfer day	
Day 3 <sup>b</sup>	32 (45.70)
Day 5	38 (54.30)
Embryos transferred	2.57 $\pm$ 0.77

Note: Data is represented as either mean  $\pm$  SD or n (%). Cryo = cryopreserved-thawed embryo; GnRH = gonadotropin releasing-hormone; ICSI = intracytoplasmic sperm injection.

<sup>a</sup> One patient had heterologous cryopreserved embryos transferred from another IVF unit, and the stimulation data were missing.

<sup>b</sup> Assisted hatching was performed in all day-3 transfers.

Vela. IVF-conceived monozygotic pregnancies. Fertil Steril 2011.

Overall, we had two cases with a triple MZ split (three fetal poles with cardiac activity within a single sac): one of the quadruplets and the quintuplet.

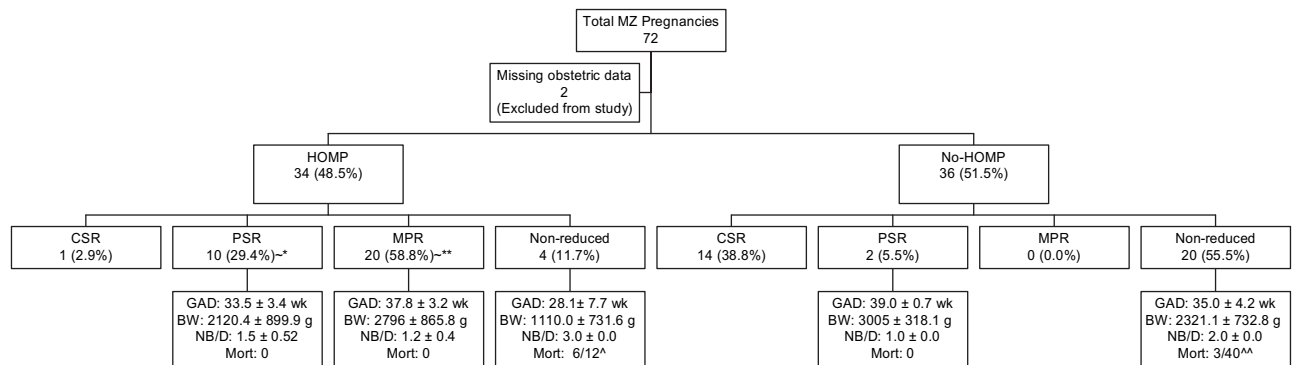
Regarding pregnancy reduction, out of 70 MZ pregnancies, the MZ component completely self-reduced in 21 cases (30%) and partially self-reduced in three cases (4.2%); the singleton component was spontaneously reduced in four cases (5.7% overall; 11.7% HOMP). Spontaneous reduction of at least one of the fetuses occurred in 38.5% of all MZ pregnancies: 32.3% of HOMP and 44.4% of non-HOMP. In the HOMP group (34 cases), only one pregnancy was completely lost (the complete MZ component was lost before discharge, and the singleton component was a late fetal demise). In the non-HOMP group, 16 pregnancies spontaneously reduced, with 87.5% (14 out of 16) of these spontaneous reductions representing a complete pregnancy loss. The only two patients who had a partial MZ spontaneous reduction in the non-HOMP group delivered at 39.5 and 38.5 weeks, respectively.

Table 2 shows the comparisons of the pregnancy outcomes by MZ pregnancy type (HOMP vs. non-HOMP). There were no statistically significant differences regarding gestational age at delivery, birth weight, or perinatal death per newborn. Owing to spontaneous and therapeutic reductions, the number of newborns per delivery and the pregnancy loss rate were statistically significantly lower in HOMP. The take-home baby rate was statistically significantly higher in this same group.

By the time of discharge from the IVF clinic, 26 out of 34 (70.5%) in the HOMP group still had at least three viable fetuses, and the maternal-fetal medicine specialist recommended a MPR; three (11.5%) had later spontaneous reductions, four (15.4%) refused the reduction procedure, and 19 (73.1%) underwent MPR. All MPRs reduced the complete MZ component of the pregnancy, and no complications were reported during any of the procedures. Two of the electively reduced pregnancies had a triple MZ split, one of

**FIGURE 1**

Pregnancy outcomes by fetal number and reduction status of MZ pregnancies conceived by in vitro fertilization. One patient had both a PSR and a MPR and was included in both groups. \*Seven MZ and three singletons were reduced. \*\*All reduced the MZ twins. ^Six neonatal deaths occurred for extreme prematurity. ^^ One stillbirth occurred at term and two neonatal deaths for extreme prematurity. BW = birth weight (grams); CSR = complete spontaneous reduction; GAD = gestational age at delivery (weeks); HOMP = high-order multiple pregnancy; MPR = multifetal pregnancy reduction; Mort = mortality; MZ = monozygotic; NB/D = newborns per delivery; PSR = partial spontaneous reduction.



Vela. IVF-conceived monozygotic pregnancies. Fertil Steril 2011.

them accompanied by a singleton fetus (quadruplet) and the other by two singleton fetuses (quintuplet). All patients who underwent a MPR delivered at least one healthy baby.

Table 3 displays the prenatal outcomes of MZ HOMP based on the reduction status. Outcomes were compared according to whether the pregnancy was not reduced, was spontaneously reduced, or was electively reduced. A statistically significant difference favoring fetal reduction (either spontaneous or elective) was seen when evaluating the number of newborns per delivery, gestational age of delivery, birth weight, perinatal death, and take-home baby rate (see Table 3 for details).

**DISCUSSION**

Monozygotic pregnancies conceived by ART are often more complicated than spontaneously conceived MZ pregnancies. As previously mentioned, IVF pregnancies themselves have a higher risk of ad-

verse obstetric outcome, and the higher incidence of multiple pregnancies conferred by these technologies also contributes to these risks. Although many studies have been published assessing the incidence and etiology of MZ twinning in IVF, to our knowledge, no previous study has focused on evaluating the outcome of this complex subset of MZ pregnancies.

According to our data, the incidence of MZ pregnancies after IVF is 1.89% of all clinical pregnancies and 2.07% of all pregnancies with cardiac activity. This is similar to what other investigators have reported in similar clinical settings (12–17). We classified a pregnancy as being MZ when more than one fetal pole with cardiac activity was seen in a single gestational sac or when the total number of fetal poles with cardiac activity was greater than the total number of embryos transferred. As previously discussed by Blickstein (18), the actual incidence of MZ twinning is very difficult to assess, particularly after ART. Considering our

**TABLE 2**

**Pregnancy outcomes by type of monozygotic pregnancy.**

Outcome	HOMP (n = 34)	Non-HOMP (n = 36)	P value
Spontaneous reduction <sup>a</sup>	11/34 (32.3)	16/36 (44.4)	.42
Multifetal pregnancy reduction <sup>a</sup>	20/34 (58.8)	0/36 (0)	.0001
No reduction <sup>a</sup>	4/34 (11.7)	20/36 (55.5)	.0003
Complete pregnancy loss <sup>a</sup>	1/34 (2.9)	14/36 (38.8)	.0007
Newborns/delivery <sup>b</sup>	1.5 ± 0.7	1.9 ± 0.2	.01
Gestational age at delivery (wk) <sup>b</sup>	35.7 ± 4.9	35.3 ± 4.2	.8
Birth weight (g) <sup>b</sup>	2,226.5 ± 1,070.7	2,353.8 ± 731.4	.5
Perinatal death/newborn <sup>a</sup>	6/50 (12)	3/42 (7.1)	.6
Take-home baby rate <sup>a</sup>	31/34 (91.1)	21/36 (58.3)	.004

Note: Data is represented as either mean ± SD or n (%). HOMP = high-order multiple pregnancy.

<sup>a</sup> Results presented as number and percentage.

<sup>b</sup> Results presented as mean ± standard deviation.

Vela. IVF-conceived monozygotic pregnancies. Fertil Steril 2011.

TABLE 3

## Perinatal outcomes of monozygotic high-order multiple pregnancies by reduction status.

	Not reduced (n = 4)	Spontaneous reduction (n = 11) <sup>a</sup>	Multifetal pregnancy reduction (n = 20) <sup>a</sup>
Newborns/delivery <sup>b</sup>	3.0 ± 0.0	1.3 ± 0.6	1.2 ± 0.4
Gestational age (wk) <sup>b</sup>	28.1 ± 7.7	33.5 ± 3.4	37.8 ± 3.2
Birth weight (g) <sup>b</sup>	1,110.0 ± 731.6	2,120.4 ± 899.9	2,796 ± 865.8
Perinatal death/newborn <sup>b</sup>	6/12 (50)	0/15 (0)	0/24 (0)
Take-home baby rate <sup>b</sup>	2/4 (50)	10/11 (90.9)	20/20 (100)

Note: Data is represented as either mean ± SD or number (%).

<sup>a</sup> One patient had both spontaneous reduction and multifetal pregnancy reduction and was accounted for in both groups.

<sup>b</sup>  $P < .05$ .

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methodology, we recognize that some early-splitting dichorionic MZ pregnancies could have been misdiagnosed as dizygotic pregnancies and were, therefore, not included in the study. Although, theoretically, early splitting happens before postconception day 5, no zygote or inner cell mass split was identified in any of the embryos transferred. In patients having two or more embryos transferred it, may be difficult to detect the zygosity of a multiple implantation if the number of sacs seen in an early ultrasound is lower or equal to the number of embryos transferred. Fingerprinting of placental DNA by highly polymorphic marker analysis is considered the gold standard for assessing zygosity in multifetal pregnancies (19). This technology could be useful to overcome this situation in further studies aiming to determine the true zygosity of IVF-conceived multiple pregnancies. On the other hand, we believe that many early MZ splits might have not been included in the study, and some biochemical or clinical pregnancies could have been MZ and were not accounted for, because no fetal heartbeat was ever detected. Often-cited population-based studies on determining the incidence of spontaneous MZ pregnancies recognize the zygosity at the time of delivery (20, 21). If we had limited the diagnosis of MZ to those pregnancies in which same-sex monochorionic fetuses were delivered, only 27 pregnancies (instead of 72) would have been accounted for.

Although the incidence of HOMP has been decreasing over the last years, ART is still a well-recognized risk factor for multiple gestations (22). As expected, occurrence of high-fetal-order gestations was not rare in our study. Nearly half of MZ pregnancies (48.5%) were part of the HOMP group. The great majority (73.4%) were part of a double implantation complicated by an MZ split of one of the embryos (becoming a triplet pregnancy). Two cases were complicated by a rare triple MZ split, leading to a quadruplet and a quintuplet pregnancy. In both cases, the triple MZ component of the pregnancy was therapeutically reduced, and both delivered healthy babies at term.

According to our data, spontaneous pregnancy reduction was a frequent outcome in MZ pregnancies. In fact, spontaneous reduction of at least one fetus occurred in 38.5% (27 out of 70) of cases. When comparing the complete pregnancy loss rate between HOMP and non-HOMP pregnancies, statistically significantly more complete losses occurred in the former group (2.9% vs. 38.8%,  $P = .0007$ ). In our experience, the presence of an extra singleton pregnancy accompanying the MZ pregnancy appeared to offer

some protection from complete fetal demise. The take-home baby rate was statistically significantly higher in the HOMP group when compared with the non-HOMP group (91.1% vs. 58.3%,  $P = .004$ ). This phenomenon has been previously reported by other investigators in non-MZ pregnancies (23–26).

When we compared the perinatal outcomes of MZ pregnancies by their initial fetal number (e.g., HOMP vs. non-HOMP), no statistically significant difference was found regarding gestational age at delivery, birth weight, or perinatal death per newborn. While making this comparison, it is important to consider that most pregnancies in the HOMP group (27 out of 34; 79.4%) had the MZ component either spontaneously or therapeutically reduced, thus improving the prognosis of the remaining singleton or dichorionic twin pregnancy. The newborn per delivery rate was statistically significantly lower in the HOMP group when compared with the non-HOMP group ( $1.5 \pm 0.7$  vs.  $1.9 \pm 0.2$ ,  $P = .01$ ) as a consequence of the higher rate of reduction for singleton pregnancies in the first group.

The increased risk, conveyed by HOMP, of severe prematurity and associated morbidity and mortality is well recognized by maternal–fetal specialists. Many recommend MPR of HOMP to a singleton or twin pregnancy and have found improved outcomes (27–29). In our center, all patients who have three viable fetuses at the time of discharge are referred to a maternal–fetal medicine specialist to further evaluate their case and to counsel the patient regarding the risks and benefits of performing a MPR. Our data clearly show a statistically significantly improved clinical outcome after spontaneous or therapeutic reduction of HOMP. In fact, pregnancies undergoing a MPR of the MZ component of pregnancy had a take-home baby rate of 100%.

Even though ours is the largest series comprehensively evaluating the outcome of IVF-conceived MZ pregnancies, the conclusions must be taken with caution because the number of participants was limited. Further multicenter prospective studies, with a larger number of patients and more detailed perinatal reports including DNA fingerprinting, are advised.

Monozygotic splitting is encountered in a small but important number of ART-derived pregnancies. The prognosis of these patients is poor, particularly for single-implantation MZ pregnancies and nonreduced HOMP. Patients who do not spontaneously reduce a MZ HOMP by 12 weeks may benefit from therapeutically reducing the MZ component of the pregnancy.

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