

# Prophylactic cervical cerclage, fully embedded, for twin pregnancies following fertility treatment

L. Mamas<sup>1</sup>, E. Mamas<sup>1</sup>

<sup>1</sup>Neogenesis IVF Centre, Marousi, Athens (Greece)

## Summary

**Purpose of Investigation:** With the advent of fertility treatment the number of twin gestations has increased considerably. These pregnancies are associated with many maternal and perinatal complications, mainly due to prematurity. The aim of this study was to assess the effectiveness of a fully embedded prophylactic vaginal cervical cerclage in reducing the rate of prematurity in twin pregnancies following ART. **Materials and Methods:** A prophylactic vaginal cervical cerclage was applied in forty three twin pregnancies conceived following fertility treatments. The cerclage suture was fully embedded under the vaginal mucosa in order to minimize the risk of infection. **Results:** The mean gestational age at delivery was 35+4 weeks and the mean delivery weight was 2,238 grams. No differences between the type of fertility treatment used was noted in the outcome measures studied. **Conclusion:** Twin pregnancies conceived with the aid of fertility treatment, benefited from the application of a prophylactic vaginal cervical cerclage.

**Key Words:** Cervical cerclage; Twins; Premature delivery; Fertility treatment; ART.

## Introduction

Over the last 40 years, the rate of multiple pregnancies has increased considerably mainly due to the wider use of assisted reproductive technologies: ART, e.g. IVF, intrauterine insemination (IUI) and controlled ovarian stimulation (COS). Based on the latest published data of the European Society of Human Reproduction and Embryology (ESHRE), in the year 2014, 17.0% of the combined IVF and intracytoplasmic sperm injection (ICSI) cycles and 7.7% of the cycles following IUI resulted in twin gestations [1]. In the United States, according to the Centre of Disease Control (CDC), in 2015, 19,6% of ART conceived infants were twins [2].

Multiple gestations are always considered high-risk due to the increased incidence of maternal and neonatal complications [3]. A high risk of perinatal complications is also noted mainly due to prematurity and low birth weight. It has been reported that following ART, the risk of extreme preterm birth (< 28 weeks) is increased [1]. Furthermore, the increase of maternal age of women opting for IVF is associated with elevated rates of obstetric complications. Studies have shown that these complications are associated with maternal characteristics and not the type of fertility treatment used [4]. However, apart from maternal factors, dizygotic twins conceived, following IVF, have a higher risk of preterm delivery when compared to non-IVF dizygotic twins [5].

A significant increase in the number of infants requiring stay in the neonatal intensive care unit (NICU) has been observed. Management of premature multiple deliveries, apart from the associated health risks, is also associated with increased medical costs. In the US, it has been estimated that the cost of preterm deliveries following ART is approximately one billion US dollars annually [6]. Moreover, the prevalence of cerebral palsy (CP), one of the most severe neonatal complications, has been reported to be higher in premature deliveries [7]. It is therefore, of great importance to apply effective ways to reduce the prematurity rate in twin pregnancies.

Throughout the years, several methods have been introduced in order to reduce the prematurity rate in multiple pregnancies and therefore minimize the complications associated, with varying success rates. Scientists have reported conflicting results regarding bed rest. Following antepartum bed rest, a slight decrease in the number of small for gestational age (GA) neonates was noted, however, pregnant women showed a higher rate of depression symptoms [8]. More recent studies have concluded that bed rest in hospital or at home shows no improvement in premature deliveries [9].

Vaginal progesterone has been shown to be beneficial in high-risk singleton pregnancies [10], however, in twin pregnancies, vaginal progesterone administration does not prevent preterm delivery [11, 12].

Published: 15 April 2020

The Arabim cervical pessary has been used as a tool for preventing preterm delivery. One of its main advantages is that its insertion is non-invasive, it is an easy procedure, and does not require anaesthesia [13].

Its efficacy is controversial and under investigation. A recent randomized controlled trial that investigated the routine use of pessary placement in twin pregnancies, failed to show a reduction in the rate of spontaneous early preterm birth [14]. Shirodkar and McDonald introduced the vaginal cervical cerclage in the 1950s [15, 16]. Their aim was to use a suture in order to reinforce the cervix during pregnancy, increase its mechanical stretch, and therefore avoid dilatation and premature delivery. In 1965, Benson and Durfee were the first to describe a transabdominal cervical cerclage (TAC) for cases that vaginal cerclage was difficult to perform mainly due to anatomical difficulties of the cervix [17]. In this study, the authors investigated the use of prophylactic vaginal cervical cerclage in twin pregnancies conceived with the aid of fertility treatments using a modified Shirodkar operation. The suture and the knot of the suture were fully embedded under the vaginal mucosa in order to reduce the rate of complications associated with infection such as, chorioamnionitis and premature rupture of the membranes. The present authors' goal was to investigate whether this prophylactic vaginal cerclage would have a positive effect on neonatal delivery weight, gestational age at delivery, rates of admission and length of stay in the NICU.

## Materials and Methods

From 2003 to 2017, 43 women with twin gestations following ICSI, intrauterine tuboperitoneal insemination (IUTPI), a modified IUI procedure [18] and COS were included in the study. Women with placenta praevia and active infection were excluded. The study protocol was approved by the local institutional review board. All women were thoroughly informed regarding the procedure, associated risks and benefits before entering the study and provided written consent.

Prophylactic vaginal cerclage was performed at 13 to 14 weeks of gestation following the nuchal translucency (NT) test. Prior to the cerclage, all women underwent screening for Chlamydia, CRP, serum measurement, and vaginal swab cultures. All operations were performed in the same private hospital setting by the same surgeon. The same technique was used in all women in this study. As mentioned before, the modification refers to the cerclage suture which was fully embedded under the vaginal mucosa. The technique was the following: the anterior and posterior lips of the cervix were grasped using Foerster tissue forceps with care not to lacerate the mucosa of the cervix.

With an empty bladder, the cervix was pulled slightly forward. A 2-cm long transverse incision in the vaginal mucosa was made on the anterior upper-third of the cervix, 2.5 cm above the external os. Blunt dissection with a peanut gauze followed in order to reveal the cervicovaginal reflection at the level of the internal cervical os. Next, a round double blunt needle, 65 mm in length and 1.6 mm diameter with polyester Mercilene tape 50 cm in length, 5 mm in width, and 0.3 mm in thickness was inserted from the right end of the incision at one o'clock under the vaginal muc-

Table 1. — Number of twin pregnancies conceived by different fertility treatments.

ICSI	23 (53.5%)
IUTPI	14 (32.5%)
COS	6 (14%)
Total	43

ICSI: intracytoplasmic sperm injection, IUTPI: intrauterine tuboperitoneal insemination, COS: controlled ovarian stimulation.

osa around the cervix and below the sacrouterine ligament at the level of the internal cervical os and exited at the posterior cervix at 6 o'clock. About 20 cm of the polyester tape was pulled to allow for free movements.

The round needle was inserted again at 6 o'clock below the sacrouterine ligament and exited from the left end of the original incision. The suture was securely tied anteriorly. Finally, the knot of the suture was buried under the vaginal mucosa which was approximated using a continuous absorbable 2-0 prolene suture. Similarly, the suture at the posterior cervix (6 o'clock) was buried as well. All women remained in hospital overnight for monitoring and were then followed up as outpatients. Monthly CRP and white blood count serum measurements were performed to monitor for signs of infection. Pregnancies were then routinely monitored by ultrasound. Amniocentesis was performed in 13 of the 43 women as per protocol after the completion of the second trimester ultra-sound without any complications.

Antenatal corticosteroids were administered intramuscularly 48 hours prior to the planned caesarian section (CS) to promote fetal lung maturation [19]. All women delivered by elective CS to minimize possible obstetric and perinatal complications and morbidity that can be associated with vaginal delivery in twin pregnancies. The delivery date was decided after taking into consideration maternal characteristics (such as age and body mass index) and following consultation with a neonatologist but gestations did not exceed 37 weeks.

The maximum gestation period was determined at 37 weeks since a significant increase has been observed in the rate of severe maternal complications with increasing gestational age, from 1.2% at 36 weeks to 3.9% at 37 weeks and 6.4% at 38 weeks [20]. The cerclage suture was removed immediately after the CS.

## Results

A total of 43 women with twin pregnancies following fertility treatment were included in the study. All participants shared common baseline characteristics. The mean age was  $34.16 \pm 3.96$  years and the mean BMI was  $24.8 \pm 3.3$  kg/m<sup>2</sup>. The methods of fertility treatment used that resulted in twin pregnancies are presented in Table 1. All twin pregnancies were dichorionic, diamniotic.

Over the 14-year study period, a total of 86 neonates were delivered. The mean neonatal delivery weight was  $2,238 \pm 329$  grams with a mean weight for first and second neonate delivered, 2,315 and 2,161 grams respectively.

All the pregnancy and neonatal characteristics are presented in Table 2. The mean GA was 35 + 4 weeks and was very similar across the three ART method groups ranging from 32 + 3 to 36 + 6 weeks. 55.8% of the neonates (49 of

Table 2. — Pregnancy and neonatal characteristics of twin pregnancies treated with prophylactic vaginal cervical cerclage.

	ART method			Neonatal gender	
	IVF	IUTPI	COS	Female	Male
Neonates (n)	46	28	12	48	38
Birthweight (g)	2213	2231	2347	2190	2298
GA (weeks)	35+1	35+6	35+5	N/A	
NICU admissions (n)	26 (56%)	16 (57%)	7 (58%)	28	21
Length of NICU stay (days)	11	10	12	13	11

GA: gestational age, NICU: neonatal intensive care unit.

the 86) required NICU admission with an average length of stay of  $7 \pm 8$  days. No significant differences were observed for delivery weight, GA, NICU admissions, and length of stay for the neonates among the three ART method groups. Overall, the male neonates weighed more than the female, but no other significant differences were noted between the two sexes.

## Discussion

Twin gestations are associated with neonatal prematurity, the rate of which increases following ART [21]. Studies have shown that pregnancies conceived following COS as well as extended embryo culture to the blastocyst stage [22] are associated with higher rates of prematurity. Moreover, multiple pregnancies are associated with elevated health risks for both the mother and the newborn, higher NICU admissions, and total cost of treatment [23].

Several methods have been proposed with the aim to increase the GA, including bed rest, progesterone administration, and the Arabim cervical pessary. Unfortunately, none of the above methods have shown true benefit. This study describes the application of a fully embedded prophylactic vaginal cervical cerclage, in order to increase the GA in twin pregnancies achieved following fertility treatment. This technique is based on the Shirodkar technique described more than 60 years ago. Both Shirodkar and McDonald have described methods of vaginal cervical cerclage, however the Shirodkar technique shows a greater increase in cervical length when measured ultrasonographically [24], as well as better results in the prevention of late preterm birth and neonatal respiratory distress syndrome [25]. The main difference between the classic Shirodkar and the proposed vaginal cervical cerclage technique, described in this study, is the fact that the cerclage suture is fully embedded under the vaginal mucosa in order to reduce the chance of infection.

The beneficial effect of prophylactic cerclage in multiple pregnancies was first reported in 1999, when Elimian *et al.* showed that prophylactic cerclage in triplet pregnancies reduced the incidence of extremely low birth weight neonates and the majority of the pregnancies were delivered after 31 weeks of gestation [26].

A recent RCT by Shehata *et al.* assessed the effect of prophylactic vaginal cerclage in a total of 120 ICSI twin pregnancies. Of those pregnancies, 80 had prophylactic cerclage and 40 did not. The mean gestational age in cerclage pregnancies was  $34.84 \pm 1.71$  weeks and in no-cerclage pregnancies it was  $32.65 \pm 2.56$  weeks, and the mean weight was  $2,313 \pm 419.81$  and  $1,828 \pm 603.34$  grams, respectively [27]. Cervical shortening is often reported in multiple pregnancies [28]. It has been shown, however, that ultrasound monitoring in twin pregnancies delivered preterm, shows dynamic and rapid changes of cervical length compared to those delivered at term [29]. Therefore, the obstetrician should not rely solely on ultrasound monitoring of cervical length in multiple pregnancies as changes may be unpredictable. Emergency cerclage has been used in cases of multiple pregnancies where cervical length is reduced at critical level. Gupta *et al.*, however, did not show a good outcome in twin pregnancies where emergency cerclage had been applied [30].

The low success rate and possible complications of emergency cervical cerclage such as, chorioamnionitis and premature rupture of the membranes further supports the need for a prophylactic elective alternative solution.

The technique presented in this study, was applied in 43 women with twin pregnancies achieved following fertility treatment (COS, IUI, and IVF) at 13 to 14 weeks of gestation. It was decided to place the suture after the completion of the NT and nasal bone assessment or the newer non-invasive prenatal test (NIPT). Following the procedure, all women in the study remained in hospital overnight for monitoring. Studies have shown that, if the procedure is performed in an outpatient setting, there is a higher rate of premature contractions, whereas cases where women remained in hospital had a higher rate of delivery of a live neonate [31]. Of the 43 pregnant women included in this study, only one showed signs of infection with an increase in CRP level at 18 weeks of gestation that is, four weeks following the procedure and was treated conservatively with antibiotics. The rate of infection reported in this study is considerably lower than that reported in the published literature; moreover, studies have also shown that application of the vaginal cervical cerclage late in the second trimester of the pregnancy, is associated with increased risk

of chorioamnionitis and premature rupture of the membranes [32], and it was thus decided to perform the procedure early in the second trimester to avoid the above complications. All women received corticosteroids for fetal lung maturation 48 hours before the CS delivery [19]. In the present study group, only one woman had preterm premature rupture of the membranes at 32 weeks gestation.

The presence of the cerclage however, allowed the authors to delay delivery for 48 hours in order to administer corticosteroids to allow for lung maturation and to possibly decrease the length of NICU stay. The mean delivery weight of the neonates in this study was  $2,238 \pm 329$  grams and more specifically for twins A and B, 2,315 and 2,161 grams, respectively. The average GA at delivery was  $35+4$  weeks  $\pm 7$  days. In 2014, the European IVF Monitoring Consortium reported 100,465 deliveries from 382,517 IVF and ICSI embryo transfers and of those 17% were multiple gestations. In these, the risk of extreme preterm birth (GA 20-27 weeks) and very preterm birth (GA 28-32 weeks) in twin pregnancies was 4.1% and 15.5%, respectively [1].

Based on these European data, the proposed method could aid more than 6,800 neonates annually, to be delivered at a safer gestational age. Furthermore, in the US, in 2015, the rate of very low birth weight (< 1500 grams) ART twins was 8.7%. Regarding GA, the rate of preterm birth (< 37 weeks) and very preterm birth (< 32 weeks) was 61% and 10.5%, respectively [2]. If we extrapolate all the above data, and given that globally around 500,000 neonates conceived through ART are delivered each year, it can be estimated that more than 30,000 twin neonates will be premature [33]. When we combine the twin pregnancies conceived through IUI and COS, we expect the number of premature twin neonates to double. Therefore, it can be concluded that application of the fully embedded prophylactic vaginal cervical cerclage may offer the chance to twin neonates to be delivered at an average acceptable delivery weight of 2,238 grams and at about  $35 + 4$  weeks that is, very close to term and therefore avoid the complications of prematurity.

Regarding NICU admissions, in the present study, 55% of the twin neonates required admission in intensive care. The mean ( $\pm$  standard deviation) length of stay in NICU in our study was  $7 \pm 8$  days. A study examining the neonatal outcome of IVF/ICSI twins versus twins conceived naturally showed that the average number of days spent in the NICU of the IVF/ICSI twins was 19.8 days [34].

In the present study the mean  $\pm$  standard deviation length of stay in NICU of twins conceived through IVF/ICSI was  $7 \pm 8$  days, that is, 12.8 days less than that reported by Pinborg *et al.* [34], emphasizing the positive effect of the prophylactic cerclage placement. It is also important to note that in the present study, many of the neonates were admitted in the NICU as a precaution, to be monitored and remained in hospital only for a few days.

As mentioned above, the incidence of cerebral palsy, a

major complication of premature neonates, increases with prematurity. The prevalence of CP in neonates has been reported to be as high as 14.6% at 22 to 27 weeks' gestation, 6.2% at 28 to 31 weeks, and 0.7% at 32 to 36 weeks, compared to 0.1% at term infants [7]. The cost of care of neonates born is high, including healthcare, productivity, and social costs [35]. Increasing GA, therefore, reduces the chance of CP in the neonate born, highlighting further the benefit of prophylactic cerclage. It may be argued that one of the best ways to avoid multiple pregnancies following IVF is the transfer of fewer embryos, with single embryo transfer (SET) being the optimal way. This however, is usually applied in women < 36 years of age, that is a fraction of the IVF cycles performed in a Fertility Centre [36]. Recently, it has been reported that even with SET, the chance of achieving a twin pregnancy due to zygotic splitting is 1.56%, which is still higher than that of naturally occurring twin pregnancies [37]. Moreover, couples opting for IVF are instigated by a powerful urge to become parents and welcome the possibility of multiple pregnancies, despite the associated risks (38). Although SET is an option in IVF cycles, there is no available solution in IUI and COS cycles, further supporting the need for a prophylactic measure to ensure the wellbeing of both the mother and fetuses in multiple pregnancies. One of the main advantages of the present technique is that all women were able to avoid bed rest and thus the psychological and socioeconomic issues associated with it, allowing them to remain active throughout their pregnancy. Although this is a report of a limited number of twin pregnancies, the authors believe that the benefit of the application of the modified, fully embedded, prophylactic vaginal cerclage can be made apparent. Application of the technique in a larger cohort of cases is needed to confirm these encouraging results.

### Acknowledgment

The authors would like to thank all the doctors and staff at the NICU unit of the IASO Maternity Hospital, Athens, Greece and Thalia Mamas for her valuable input.

### References

- [1] De Geyter C., Calhaz-Jorge C., Kupka M.S., Wyns C., Mocanu E., Motrenko T., *et al.*: "European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE): "ART in Europe, 2014: results generated from European registries by ESHRE: The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE)". *Hum Reprod.*, 2018, 33, 1586.
- [2] Sunderam S., Kissin D.M., Crawford S.B., Folger S.G., Boulet, S.L., Warner L., Barfield W.D.: "Assisted Reproductive Technology Surveillance — United States, 2015". *MMWR Surveill. Summ.*, 2018, 67, 1.
- [3] Santolaya J., Faro R.: "Twins – twice more trouble?" *Clin. Obstet. Gynecol.*, 2012, 55, 296.
- [4] Bamberg C., Fotopoulou C., Neissner P., Slowinski T., Dudenhausen J.W., Proquitté H., *et al.*: "Maternal characteristics and twin gestation outcomes over 10 years: impact of conception methods". *Fertil.*

- Steril.*, 2012, 98, 95.
- [5] Källén B., Finnström O., Lindam A., Nilsson E., Nygren K.G., Olausson P.O.: "Selected neonatal outcomes in dizygotic twins after IVF versus non – IVF pregnancies". *BJOG*, 2010, 117, 676.
- [6] Bromer J.G., Ata B., Seli M., Loodwood C.J., Seli E.: "Preterm deliveries that result from multiple pregnancies associated with assisted reproductive technologies in the USA: a cost analysis". *Curr. Opin. Obstet. Gynecol.*, 2011, 23, 168.
- [7] Himpens E., Van den Broeck C., Oostra A., Calders P., Vanhaesebrouck P.: "Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review". *Dev. Med. Child. Neurol.*, 2008, 50, 334.
- [8] Maloni J.A., Margevicius S.P., Damato E.G.: "Multiple gestation: side effects of antepartum bed rest". *Biol. Res. Nurs.*, 2006, 8, 115.
- [9] Da Silva Lopes K., Takemoto Y., Ota E., Tanigaki S., Mori R.: "Bed rest with and without hospitalisation in multiple pregnancy for improving perinatal outcomes". *Cochrane Database Syst Rev.*, 2017, 3, CD012031.
- [10] Sotiriadis A., Papatheodorou S., Makrydimas G.: "Perinatal outcome in women treated with progesterone for the prevention of preterm birth: a meta-analysis". *Ultrasound Obstet. Gynecol.*, 2012, 40, 257.
- [11] Hernandez W.R., Francisco R.P.V., Bittar R.E., Gomez U.T., Zugaib M., Brizot M.L.: "Effect of vaginal progesterone in tocolytic therapy during preterm labor in twin pregnancies: Secondary analysis of a placebo-controlled randomized trial". *J. Obstet. Gynaecol. Res.*, 2017, 43, 1536.
- [12] Dodd J.M., Grivell R.M., O'Brien C.M., Dowswell T., Deussen A.R.: "Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy". *Cochrane Database System Rev.*, 2017, 10, CD012024.
- [13] Carreras E., Arévalo S., Bello-Muñoz J.C., Goya M., Rodó C., Sanchez-Duran M. A., et al.: "Arabin cervical pessary to prevent preterm birth in severe twin-to-twin transfusion syndrome treated by laser surgery". *Prenat. Diag.*, 2012, 32, 1181.
- [14] Nicolaides K.H., Syngelaki A., Poon L.C., de Paco Matallana C., Plasencia W., Molina F.S., et al.: "Cervical pessary placement for the prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial". *Am. J. Obstet. Gynecol.*, 2016, 214, e1.
- [15] Shirodkar J.N.: "A new method for operative treatment of habitual abortions in the second trimester of pregnancy". *Antiseptic*, 1955, 52, 299.
- [16] McDonald I.A.: "Suture of the cervix for the inevitable miscarriage". *J. Obstet. Gynecol. Br. Emp.*, 1957, 64, 346.
- [17] Benson C.R., Durfee R.B.: "Transabdominal cervicouterine cerclage during pregnancy for the treatment of cervical incompetency". *Obstet. Gynecol.*, 1965, 25, 145.
- [18] Mamas L.: "Comparison of fallopian tube sperm perfusion and intrauterine tuboperitoneal insemination: a prospective randomized study". *Fertil. Steril.*, 2006, 85, 735.
- [19] Magann E.F., Haram K., Ounpraseuth S., Mortensen J.H., Spencer H.J., Morrison J.C.: "Use of antenatal corticosteroids in special circumstances: a comprehensive review". *Acta Obstet. Gynecol. Scand.*, 2017, 96, 395.
- [20] Yamamoto R., Ishii K., Muto H., Ota S., Kawaguchi H., Hayashi S., Mitsuda N.: "Incidence of and risk factors for severe maternal complications associated with hypertensive disorders after 36 weeks' gestation in uncomplicated twin pregnancies: A prospective cohort study". *J. Obstet. Gynaecol. Res.*, 2018, 44, 1221.
- [21] Moini A., Shiva M., Arabipour R., Hosseini R., Chehrizi M., Sadeghi M.: "Obstetric and neonatal outcomes of twin pregnancies conceived by assisted reproductive technology compared with twin pregnancies conceived spontaneously: a prospective follow – up study". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2012, 165, 29.
- [22] Kalra S.K., Radcliffe S.J., Barnhart K.T., Coutifaris C.: "Extended embryo culture and an increased risk of preterm delivery". *Obstet. Gynecol.*, 2012, 120, 69.
- [23] Ericson A., Nygren K.G., Olausson P.O., Källén B.: "Hospital care utilization of infants born after IVF". *Hum. Reprod.*, 2002, 17, 929.
- [24] Rozenberg P., Sénat M.V., Gillet A., Ville Y.: "Comparison of two methods of cervical cerclage by ultrasound cervical measurement". *J. Matern. Fetal Neonatal Med.*, 2003, 13, 314.
- [25] Wong C.H., Chen C.P., Wang K.G., Sun F.J., Chen C.Y.: "Comparison of two cervical cerclages for the prevention of preterm birth and neonatal complications". *J. Matern. Fetal Neonatal Med.*, 2017, 30, 551.
- [26] Elimian A., Figueroa R., Nigam S., Verma U., Tejani N., Kirshenbaum N.: "Perinatal outcome of triplet gestation: does prophylactic cerclage make a difference?" *J. Matern. Fetal Med.*, 1999, 8, 119.
- [27] Ayman S., Hesham B., Naglaa H., Maher A.H.: "Prophylactic Cerclage in ICSI Twins: To Do or Not to Do? A Randomized Controlled Study". *Womens Health Gynecol.*, 2016, 2, 042.
- [28] Skentou C., Souka A.P., To M.S., Liao A.W., Nicolaides K.H.: "Prediction of preterm delivery in twins by cervical assessment at 23 weeks". *Ultrasound Obstet. Gynecol.*, 2001, 17, 7.
- [29] Bergelin I., Valentin L.: "Cervical changes in twin pregnancies observed by transvaginal ultrasound during the latter half of the pregnancy: a longitudinal, observational study". *Ultrasound Obstet Gynecol.*, 2003, 21, 556.
- [30] Gupta M., Emary K., Impey L.: "Emergency cervical cerclage: predictors of success". *J. Matern. Fetal Neonatal Med.*, 2010, 23, 670.
- [31] Blair O., Fletcher H., Kulkarni S.: "A randomized controlled trial of outpatient versus inpatient cervical cerclage". *J. Obstet. Gynaecol.*, 2002, 22, 493.
- [32] Charles D., Edwards W.R.: "Infectious complications of cervical cerclage". *Am. J. Obstet. Gynecol.*, 1981, 141, 1065.
- [33] De Geyter C.: "Eight million IVF babies since the birth of the world's first in 1978". 34th Annual ESHRE Meeting, Barcelona. [https://www.focuserreproduction.eu/article/ESHRE\\_News\\_GlobalIVF8](https://www.focuserreproduction.eu/article/ESHRE_News_GlobalIVF8)
- [34] Pinborg A., Loft A., Rasmussen S., Schmidt L., Langhoff-Roos J., Greissen G., et al.: "Neonatal outcome in a Danish national cohort of 3439 IVF/ICSI and 10362 non-IVF/ICSI twins born between 1995 and 2000". *Hum. Reprod.*, 2004, 19, 435.
- [35] Kruse M., Michelsen S.I., Flachs E.M., Brønnum-Hansen H., Madsen M., Uldall P.: "Lifetime costs of cerebral palsy". *Dev. Med. Child. Neurol.*, 2009, 51, 622.
- [36] Lee A.M., Connell M.T., Csokmay J.M., Styer A.K.: "Elective single embryo transfer- the power of one". *Contracept. Reprod. Med.*, 2016, 1, 11.
- [37] Ikemoto Y., Kyroda K., Ochiai A., Yamashita S., Ikuma S., Nojiri S., et al.: "Prevalence and risk factors of zygotic splitting after 937 848 single embryo transfer cycles". *Hum. Reprod.*, 2018, 33, 1984.
- [38] Blennborn M., Nilsson S., Hillervik C., Hellberg D.: "The couple's decision-making in IVF: one or two embryos at transfer?" *Hum. Reprod.*, 2005, 20, 1292.

Corresponding Author:  
L. MAMAS, M.D.  
Neogenesis IVF Centre  
3 Kifissias Ave  
151 23 Marousi, Athens (Greece)  
e-mail: leon.mamas@gmail.com