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Assisted Reproduction and Preterm Birth

Offer Erez[1], Ruth Beer-Weisel[1], Tal Rafaeli-Yehudai[1],
Idit Erez-Weiss[2] and Moshe Mazor[1]
*[1]Department of Obstetrics and Gynecology "B" Soroka University Medical Center,
School of Medicine, Faculty of Health Sciences,
Ben Gurion University of the Negev, Beer Sheva,
[2]Department of Family Medicine, School of Medicine, Faculty of Health Sciences,
Ben Gurion University of the Negev, Beer Sheva,
Israel*

1. Introduction

Preterm parturition is a syndrome (Romero, Gomez *et al.*, 1997; Romero R, Espinoza J *et al.*, 2004) that is one of the leading causes for perinatal morbidity and mortality. Moreover, prematurity is a leading cause for neonatal mortality, as well as short and long term morbidity. The incidence of preterm delivery is constantly increasing, crossing the 12% in the USA, and it's annual cost reached 26.2 billion US dollars in 2005, posing a huge burden on public health (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007).

Prematurity can be either spontaneous due to preterm labor with intact membranes (PTL) or preterm prelabor rupture of the chorioamniotic membranes (preterm PROM); or indicated, meaning induced preterm delivery by the medical team due to maternal (i.e. preeclampsia) or fetal (growth restriction, non-reassuring fetal heart rate tracing) indication (Goldenberg, Culhane *et al.*, 2008). The incidence of the latter group, especially after 34 weeks of gestation, is constantly rising (Ananth, Joseph *et al.*, 2005; Ananth and Vintzileos, 2006a; Ananth, Getahun *et al.*, 2006).

Emerging contributors for the increasing rate of preterm birth are assisted reproduction technologies (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). The use of infertility treatments has risen dramatically in the past 20 years; between 1996 and 2003, the number of cycles of Assisted reproductive technologies (ART) nearly doubled from 64,681 to 122,872. The number of live births resulting from conceptions achieved by the use of ARTs more than doubled from 14,507 to 35,785 (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 1980). This has been associated with the trend to delay childbearing, indeed, more than 50 percent of these women were 35 years of age or older. In recent years, an unintended consequence of the use of these technologies, multiple gestations and the increased risk for preterm delivery, has become a focus of attention, and the institute of Medicine in the USA has concluded that "Fertility treatments are a significant contributor to preterm birth among both multiple and singleton pregnancies." (Institute of

Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007).

The mechanisms in which assisted reproduction technologies increases the risk for preterm birth are still under investigation. Aside the contribution of ART to the increase number of multiple gestations (especially twins) that increases the risk for preterm delivery; The mechanisms leading to preterm delivery in singleton gestations conceived through ART have not been thoroughly investigated. Preliminary evidence suggests that some of the underlying maternal conditions that lead to infertility (i.e. inflammation and insulin resistance) may contribute to this observation.

The current chapter will explore the epidemiology, underlying mechanisms, and possible tools for the prevention of preterm delivery in pregnancies conceived by assisted reproduction.

2. Infertility: Treatments, epidemiology and trends

2.1 Definitions

The most commonly used definition of infertility is a failure to conceive after 12 months of regular, unprotected intercourse. However, existing definitions of infertility lack uniformity, rendering comparisons of prevalence between countries or over time problematic. The absence of an agreed definition also compromises clinical management and undermines the impact of research findings. Gurunath at al suggested that the definition will be based on the duration of trying for pregnancy coupled with female age. (Gurunath, Pandian *et al.*, 2011) According to the report of The Centers for Disease Control and Prevention (CDC), in 2002, 7% of married couples in which the woman was of reproductive age (2.1 million couples) reported that they had not used contraception for 12 months and the woman had not become pregnant. Many of these patients are treated by ARTs. These technologies are defined by the CDC as procedures in which the ovum and the sperm are handled in the laboratory. During the past few decades several options of ART have developed including: 1) in vitro fertilization (IVF); 2) intra-cytoplasmic sperm injection (ICSI); 3) gamete intra-fallopian transfer (GIFT) and 4) zygote intra-fallopian transfer (ZIFT) (Centers for Disease Control and Prevention 2008).

2.2 What is the magnitude of ART utilization in developed countries?

The use of infertility treatments has risen dramatically in the past 10 years and has been associated with the trend to delay childbearing. Today, over 1% of all infants born in the United States every year are conceived using ART; and the number of ART cycles performed has nearly doubled, from 87,636 cycles in 1999 to 148,055 in 2008. Similarly, the number of live-birth in 2008 (46,326) was more than twice the number recorded 1999 (21,746). Because in many of the ART pregnancies more than one infant is born alive (e.g., twins, triplets), the total number of infants born is greater than the number of live-birth. The trend in the number of infants delivered after ART cycles was in accord to the trends observed in the number of pregnancies and live-births. Thus, the number of infants born in 2008, (61,426) was more than twice than the 30,629 that were delivered in 1999 (Figure 1).

Outside the USA, The Canadian Assisted Reproductive Technologies Register (CARTR), in its 2007 annual publication, reported a 12% increase in the total number of ART cycles, and an increase in the rate of clinical pregnancies and live-birth, along with a decrease in high-order multiple births in comparison to these parameters in 2006 (Gunby, Bissonnette *et al.*,

2011). While in Europe, according to the 10th annual European Society of Human Reproduction and Embryology (ESHRE) publication the reported number of ART cycles has increased, with a marginal increase in pregnancy rates, even though fewer embryos were transferred and the multiple delivery rates have declined (1994). This report includes 20 countries, where all clinics report their activity to the IVF register. Altogether, a total of 359,110 cycles were performed in a population of 422.5 million, corresponding to 850 cycles per million inhabitants. The IVF cycles rates of clinical pregnancy per ovum aspiration and per embryo transfer were 29.0 and 32.4%, respectively; while the corresponding ICSI cycles rates were 29.9 and 33.0%, respectively (1994). In spite of the new guidelines, transferring of 2 embryos is still the most prevalent choice in the European Union.
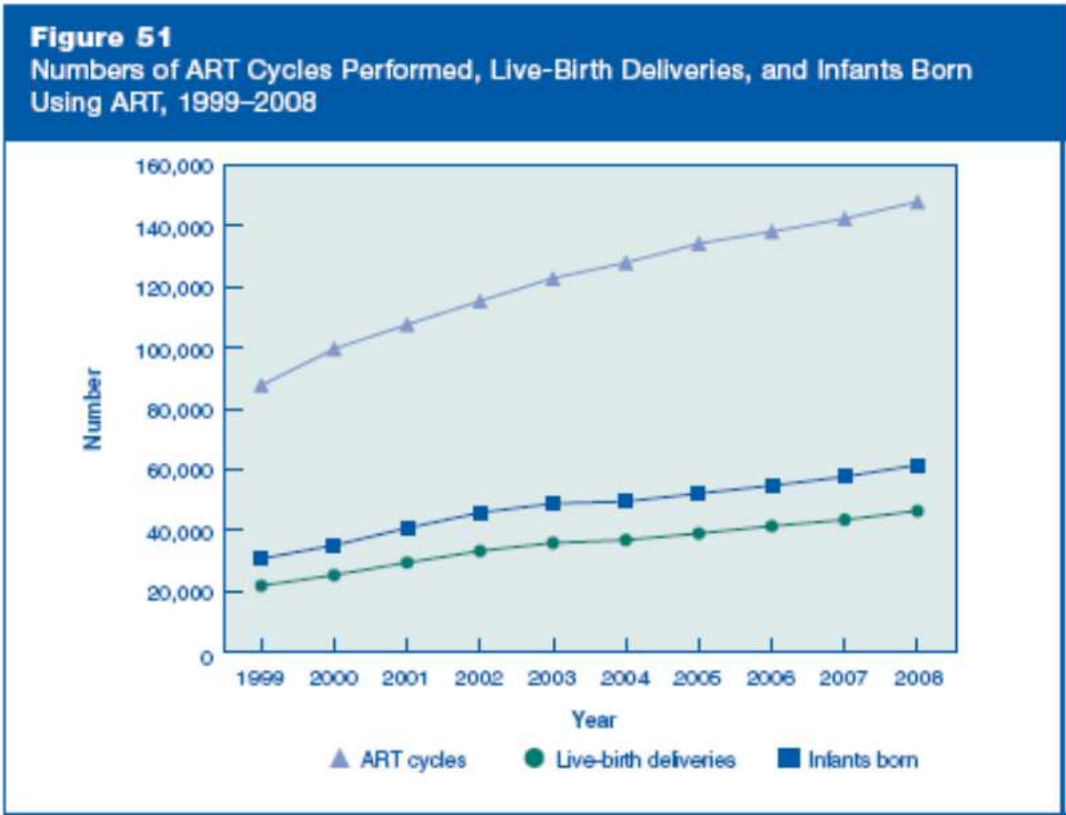

Fig. 1. Number of ART cycles performed, live-birth delivery, and infants born used ART, 1999-2008 From Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2006 Assisted Reproductive Technology Success Rates: National summary and fertilityNclinic reports. Atlanta: Centers for Disease Control and Prevention,2008.

ART often is categorized according to whether the procedure used a woman's own eggs (self) or eggs from another woman (donor) and according to whether the embryos used were newly fertilized (fresh) or previously fertilized, frozen, and then thawed (frozen). For approximately 71% of ART cycles performed in USA in 2008, self-fresh eggs or embryos were used. ART cycles that used self-frozen embryos were the next most common type, accounting for approximately 17% of the total. In about 12% of cycles, eggs or embryos were donated by another woman (Figure 2).
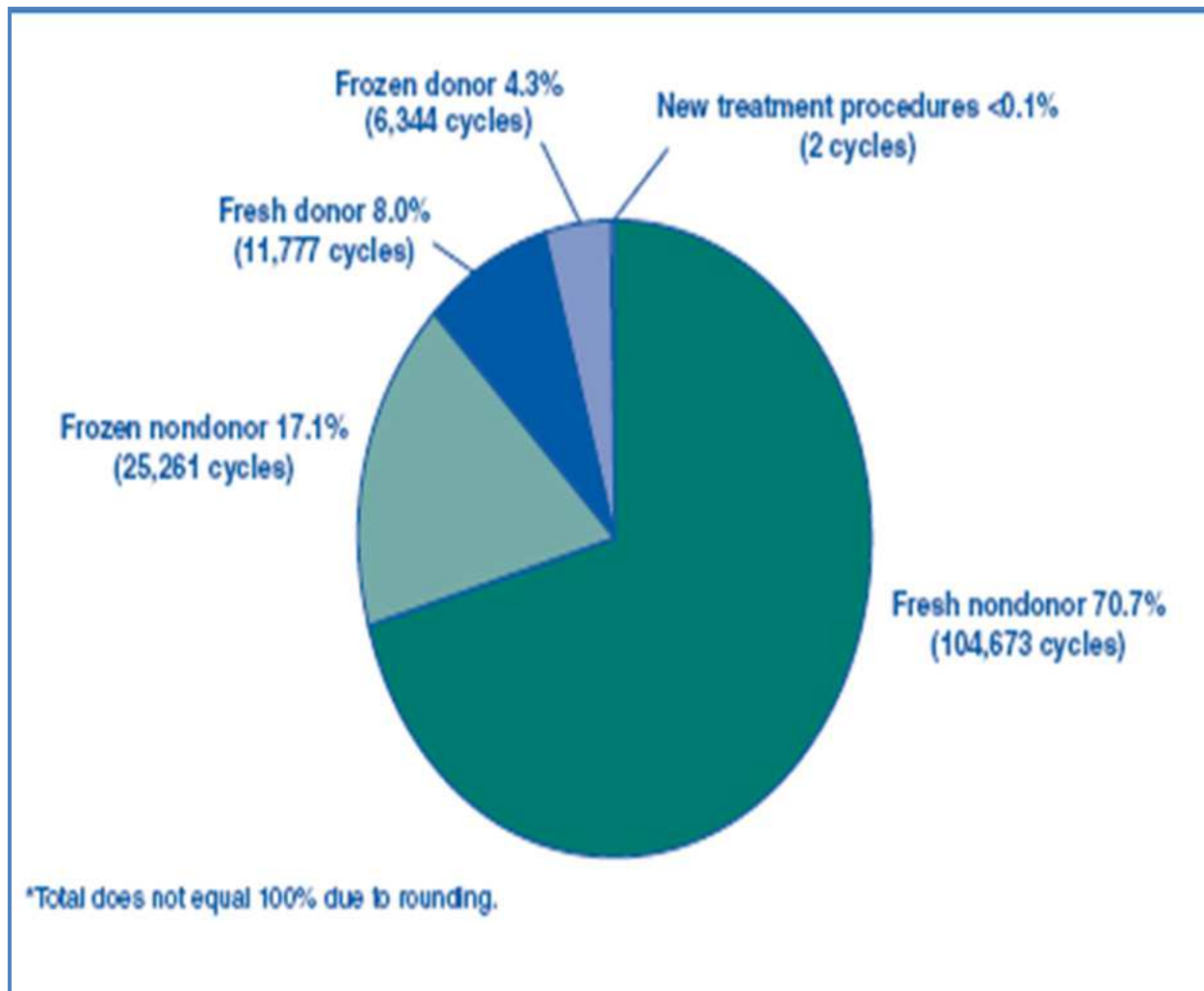
Fig. 2. Distribution of ART cycles according to the source of the ovum and whether the cycle was fresh or frozen. (CDC 2008, USA).

The average age of women using ART services in the USA in 2008 was 36. However, the largest group of women using ART services were women younger than 35, representing approximately 39% of all ART cycles performed in 2008. Approximately 21% of ART cycles were performed in women aged 35–37, 20% in women aged 38–40, 10% in women aged 41–42, 6% in women aged 43–44, and 5% among women older than 44 (Figure 4). In Europe, the age distribution of women treated with IVF varied across the continent. In some countries, more than 20% of women were aged 40 years or older (Greece, Ireland, Italy, Macedonia, Montenegro, Serbia and Switzerland), whereas in Bulgaria, Czech Republic, Lithuania, Norway, Poland, Portugal, and Ukraine <10% were 40 years or older. (ESHRE,2006)

The success rate of ART decreases with age, indeed, pregnancy rates decreased from 28.2% in women aged ≤34, to 9.6% at the age ≥40 years. A similar trend was seen for the delivery rates (26.6%, and 8.6%). In egg donation cycles, the recipients were aged 40 years or more in 50.0% of cases, in almost all countries. Pregnancy and delivery rates in oocyte recipients were comparable across different age groups. (ESHRE,2006)
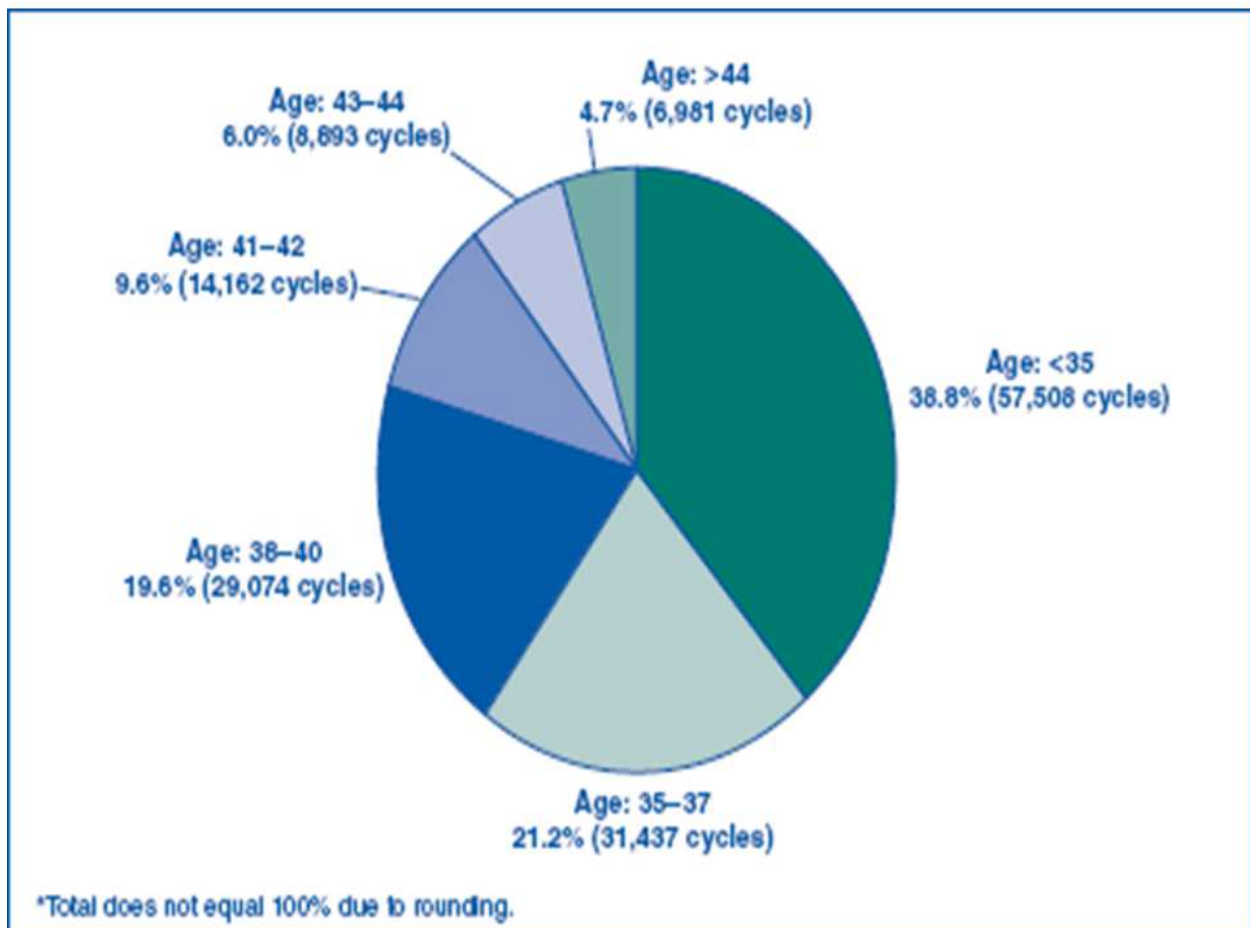
Fig. 3. Maternal age distribution among patients undergoing ART cycles. CDC 2008 USA.

3. The effect of maternal age on reproduction and pregnancy outcome

The average fertility rate (live births per 1,000 women of childbearing age 15–44 years) in USA from 1991-2008 is about 66.5, with mild fluctuations over the years. When it is divided in subgroups by maternal age, the birth rate has declined for women under 30-s on the other hand among women in their 30's- 40's the fertility rate had steadily increased from 1978 onward. In the last three decades a new group of women aged 50 and over has increased more than 10 percent annually since 1997 (Martin, Hamilton *et al.*, 2010). The trend in the fertility rate among European women is somewhat different. From the 1960s up to the beginning of the 21st century, the number of live births in the Europe declined sharply. However, from 2002 onward there has been a modest rebound in the number of live births born in this continent. As with the American women, the late increase during the last years may be, in part, attributed to a catching-up process following a general pattern of postponing the child bearing age. When women give birth later in life, the total fertility rate first indicates a decrease in fertility, followed later by a recovery (Atkinson and Marlier, 2010). For example, in Finland the rate of women giving birth after the age of 35 increased from 16.7%in 1997 to 19.2% in 2007 (Lampinen, Vehvilainen-Julkunen *et al.*, 2009). The corresponding mean maternal age in Japan between 1970 and 2000 increased from 25.6 to 28.0 years (Mathews and Hamilton, 2002).

Delaying childbearing may be attributed to several reasons, beginning with the longer life span, greater accessibility to education and career opportunities for women, and the existence of effective means of birth control (Stein, 1985; Berkowitz, Skovron *et al.*, 1990). Men and women recognized the direct relationship between older maternal age and the declined in fertility (Tough, Benzies *et al.*, 2006; Tough, Benzies *et al.*, 2007), however, there is a popular concept that IVF treatment can reverse the effects of age (Maheshwari, Porter *et al.*, 2008). Interestingly, along with acknowledgment in the success of ART there is a lack of awareness regarding the effect of maternal age over perinatal complications during pregnancy. Women are not aware of the increased risk of preeclampsia, stillbirth, caesarean delivery, multiple births and preterm delivery associated with delayed childbirth to elderly stages of life (Tough, Benzies *et al.*, 2006; Tough, Benzies *et al.*, 2007).

Postponement of motherhood beyond 35 years of age influences many aspects of reproduction from conceiving through embryonic implantation all the way until delivery. The effect of maternal age on her ability to conceive is well documented. Populations that do not use contraceptives and practice unprotected intercourse give the best estimation of the ability of normal women to conceive. Based on 10 different populations living between the 17th and the 20th Centuries that did not use contraceptives, Menken et al (Menken, Trussell *et al.*, 1986) reported that the fertility rate remains relatively stable until a woman is in her late 30s and then decreases substantially from more than 400 pregnancies per 1000 women per year at the age of 30, to only 100 pregnancies per 1000 women per year by the age of 45. The decline in fertility as a function of women's age was also demonstrated in a donor insemination programmed in which the cause of infertility was related to male factors alone and the women were assumed to be normal. Pregnancy rates at 1 year declined from 74% among women below the age of 30 years to 61.5% among women aged 31–35 years and 55.8% among women aged 36–41 years (Schwartz and Mayaux, 1982).

After conceiving, the risk of spontaneous miscarriage increases as a function of maternal age. In a prospective population-based register linkage study, involving 12,221,546 pregnancies of 634,272 Danish women from 1978 to 1992, older maternal age was a significant risk factor for spontaneous pregnancy loss irrespective of the number of previous miscarriages and parity. The risk of a spontaneous abortion in women aged 20–24 years was 8.9% and it climbed up to 74.7% in those aged 45 years or older (Nybo Andersen, Wohlfahrt *et al.*, 2000). Ben Kroon et all performed a cytogenetic evaluation for the products of conception obtained from patients with first trimester abortion who had a dilatation and curettage (D&C). The rate of embryos with aneuploidy in women aged ≥35 years was significantly higher than that of those younger than 35 years (45.7%, vs. 34.8%, respectively; P=.018) (Kroon, Harrison *et al.*, 2011). The derived rates apply to women whose only risk factor is advanced maternal age. The categories analyzed were trisomy 21 (Down's syndrome), Trisomy 18 (Edwards' syndrome), trisomy 13 (Patau's syndrome), 47XXY (Klinefelter's syndrome), 47,XXX, and a group of other clinically significant abnormalities that were considered collectively. The rate of all these chromosomal abnormalities in this study was about five per 1,000 at age 35 years, 15 per 1,000 at age 40 years, and 50 per 1,000 at age 45 years (Hook, Cross *et al.*, 1983). Savva et al (Savva, Walker *et al.*, 2010) reviewed the records of prenatal and postnatal diagnoses from seven UK regional congenital anomaly registers and two Australian registers from 1997 to 2004. These dataset included 4.5 million deliveries, of which 975 diagnosed as having trisomy 13 and 2254 had trisomy 18. In addition, the authors reported that since 1989 until 1996 there was an increase, by 13% in the

rate of trisomy 13 and by 25% in the rate of trisomy 18. These findings are consistent with those predicted to be associated with the increases in maternal age (Savva, Walker *et al.*, 2010).

The link between Down syndrome and advanced maternal age deserves special attention. This association was already reported by Penrose in the mid 1930's (Penrose, 1933; Penrose, 1934). Lately, Graves Allen et al (Allen, Freeman *et al.*, 2009) examined the origin of the meiotic error leading to the association between maternal age and chromosome 21 non-disjunction. They emphasis that the a significant association between advanced maternal age and chromosome 21 non-disjunction was restricted to meiotic errors in the egg and was not observed in sperm or in post-zygotic mitotic errors. The authors reported that the advanced maternal age was significantly associated with a higher rate of non-disjunction in both meiosis I (MI) and meiosis II (MII). Indeed, compared to mothers of euploid neonates, mothers of infants with trisomy 21 due to MI non-disjunction were 8.5 times more likely to be ≥40 years old than 20–24 years old at the birth of the index case (95% CI = 5.6–12.9). Where non-disjunction occurred in MII, mothers were 15.1 times more likely to be ≥40 years (95% CI = 8.4–27.3) (Allen, Freeman *et al.*, 2009).

Women's age has a major impact on the rate of chronic maternal diseases and pregnancy outcome. Indeed, the rate of diabetes increases with maternal age. The 2010 National Vital Statistics Reports reported that in 2007 the rate of diabetes among USA mothers under the age of 20 was 14.0 per 1,000, and it increases almost 7 times higher to 100.5 per 1,000 in women over the age of 40 (Table 1). Similar trends were reported regarding the rate of chronic hypertension. The prevalence of this disease increases from 3.9 per 1000 in women younger than 20 years old to 32.2 per 1000 in women older than 40. In contrast to the linear association between diabetes, as well as chronic hypertension and maternal age, the incidence of gestational hypertension as a function of maternal age has a U shape curve with a prevalence of 41.8 per 1000 among patients under 20 years and 50.1 per 1000 for women over 40, and the lowest incidence is between 20-35 years old. Similarly to the National Vital Statistics Reports, a different population based cohort involving 1,160,000 women delivered during a 2-year period found increased rate of preeclampsia and gestational diabetes among women aged 40 years or older in comparison to those aged 20-29 (Gilbert, Nesbitt *et al.*, 1999). Yogev et al (Yogev, Melamed *et al.*, 2010) stratified the rate of pregnancy complication according to maternal age with a special attention to women aged ≥45 years (n = 177) with an additional subgroup analysis of women aged 45-49 years with those women aged ≥50 years. Similar to previous studies the authors reported that the rates of gestational diabetes mellitus and hypertensive complications of pregnancy were increased among women aged 45 years and older.

Maternal age also influences perinatal outcome, small-for-gestational age births (SGA) are common and can have serious immediate consequences for the infant (Das and Sysyn, 2004; Salem, Levy *et al.*, 2011). They have also been associated with the development of a range of chronic diseases in subsequent adult life (Nepomnyaschy and Reichman, 2006; Barker, 2004). There is an association between maternal age and the delivery of an SGA neonate. In the FASTER trial, patients aged 35-39 years were at increased risk to a deliver low birthweight neonate (adjusted OR 1.6) (Cleary-Goldman, Malone *et al.*, 2005). In addition, Salem- Yaniv et al, in a retrospective population based study found a significant increase in low birth weight among older women (35–40 and above 40 years of age) in comparison to women younger than 35 years old (Salem, Levy *et al.*, 2011).

Maternal age	Diabetes per 1,000 live births in specified group	Chronic Hypertension per 1,000 live births in specified group
All ages	44.8	11.0
Under 20 years	14.0	3.9
20–24 years	25.9	6.4
25–29 years	42.4	9.9
30–34 years	59.5	13.6
35–39 years	78.6	20.4
40–54 years	100.5	32.2

Table 1. Number and rate of live births to mothers with selected risk factors during pregnancy, obstetric procedures, characteristics of labor and delivery, and congenital anomalies, by age and race and Hispanic origin of mother: United States, 2007. (National Vital Statistics Reports, Volume 58, Number 24, August 9, 2010)

The Human Fertilization and Embryology Authority database was examined in order to ascertain the predictors of live birth in all IVF cycles undertaken in the UK between 2003 and 2007 (n = 144,018). This study has found that the odds of low birth weight were reduced with increasing maternal age and with a history of a previous pregnancy (either spontaneous or following IVF) (Nelson and Lawlor, 2011). Similarly to these findings, Erez et al reported that among patients with twin gestation who conceived through ART the rate of preeclampsia was higher in women younger than 35 years old than in older parturient (Erez, Vardi *et al.*, 2006). These reports suggest that among patients who suffers from infertility the background maternal illness may be more severe and with clinical implication that is additive to the effect of maternal age.

Advanced maternal age also influences the rate of preterm delivery. Jacobsson et al examined the Swedish Medical Birth Register, managed by the National Board of Health and Welfare, contains data on 1,566,313 deliveries that are more than 99% of all births in Sweden during the last 15-years. The rate of preterm delivery before 37 and 34 weeks among women 20-29 were compared to those of women age 40-44 years and above 45 years (Jacobsson, Ladfors *et al.*, 2004). The authors reported that the rate of preterm birth increases with maternal age. Indeed, after adjustment to confounding factors women aged 40-44 years old had an odds ratio of 1.54 (95% CI 1.47-1.60), while those who were ≥ 45 years had an odds of 1.63 (95% CI 1.32-2.00) to deliver before 37 weeks of gestation (Jacobsson, Ladfors *et al.*, 2004). Similar data where published also by others (Cleary-Goldman, Malone *et al.*, 2005; Salem, Levy *et al.*, 2011).

Women ≥ 35 years have a significantly higher rate of fetal death than their younger counterparts. Fretts and colleagues documented that the fetal death rate decreased by more than 70 percent over the past 30 years among white Canadian women. Although the absolute stillbirth rate declined significantly for women of all ages and parity groups, older women remained at higher risk for fetal death, even after controlling for diabetes, hypertension, and placental abruption (Fretts, Schmittdiel et al., 1995). This report was in accord with other publications regarding the increased rate of fetal demise among older women (Jacobsson, Ladfors et al., 2004; Cleary-Goldman, Malone et al., 2005). In contrast, among nulliparous patients advanced maternal age was not an independent risk factor for perinatal mortality (Salem, Levy et al., 2011).

The increasing numbers of pregnancies at advanced maternal age influences the rising rate of cesarean birth. Among 57,426 primiparous women who gave birth in Victoria, Australia, in 2005 and 2006, older patients were more likely to give birth by cesarean section in comparison to younger primiparous women (Carolan, Davey et al., 2011). Salem-Yaniv at al reported that in comparison to women younger than 35 years old, those aged 35–40 have an almost a threefold increase in the rate of cesarean deliveries among nulliparous patients (38.2%) and close to a fivefold increase among women over 40 years (63.3%) (Salem, Levy et al., 2011). Similar results were published by the National Vital Statistics Reports UA. Among 4,316,233 women that delivered during the year 2007, older maternal age was associated to delivery through cesarean section (under 20 22.7% 35-39 41.8%: 40-54 47.7%) (Martin, Hamilton et al., 2010). This increasing risk of cesarean birth associated with advancing maternal age is of importance, because the proportion of women who are delaying childbearing is growing, and in addition, the cesarean delivery rate is increasing (Martin, Hamilton et al., 2010).

4. Pregnancy outcome in patients conceived through assisted reproduction

IVF pregnancies are associated with an increased risk for obstetrics complication including gestational diabetes, preeclampsia, placenta previa and neonatal intensive care admission (Shevell, Malone et al., 2005; Chen, Wen et al., 2009; Nelson and Lawlor, 2011). A prospective database from a large multicenter investigation of singleton pregnancies demonstrated that the use of IVF was associated with a significant increase in the risk to develop preeclampsia (OR 2.7; 95% CI 1.7–4.4), placental abruption (OR 2.4; 95% CI 1.1–5.2), placenta previa (OR 6.0; 95% CI 3.4–10.7), and risk of cesarean delivery (OR 2.3; 95% CI 1.8–2.9) (Shevell, Malone et al., 2005). A different prospective cohort study that included singleton IVF/ICSI pregnancies had more than 4-fold increased risk of stillbirth compared with spontaneously conceived singleton pregnancies (Wisborg, Ingerslev et al., 2010a). There is a strong evidence to support the association between IVF treatments and preterm birth. Indeed, ART are independently associated with preterm birth in singleton as well as in twin gestation.

5. The association between preterm birth and assisted reproduction

Preterm delivery is the leading cause for perinatal morbidity and mortality worldwide (Goldenberg, Culhane et al., 2008). The annual societal economic burden associated with preterm birth in the United States exceeded $26.2 billion in 2005 (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). Preterm birth is associated with short and long term maternal and fetal sequel. The

mothers are at risk of recurrent preterm birth and cardiovascular disease later in life. (Nardi, Zureik *et al.*, 2006; Smith, Pell *et al.*, 2001) The premature newborn is at risk for acute (i.e. respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage) and chronic (i.e. retinopathy of prematurity, cerebral palsy, broncho pulmonary dysplasia) illness, as well as social and behavioral maladjustment later in life. (Moster, Lie *et al.*, 2008) The prevalence of preterm birth varies from 6% to 15% of all deliveries depending on the geographical and demographical characteristics of the population tested. (Romero, Mazor *et al.*, 1994; Martin, Hamilton *et al.*, 2009; Slattery and Morrison, 2002).

In Europe the rate of preterm deliveries varies from 5% to 9% (Slattery and Morrison, 2002), while the rate of preterm birth in the United States reached 12.8% by 2006 (Martin, Hamilton *et al.*, 2009), 20% higher than in 1990. Of interest, while the rate of early (<34 weeks) preterm birth remained relatively constant (2.9% among singleton and 3.3% to 3.6% among multiple gestations) the rate of late preterm birth (34-37 weeks) increased among singleton by 19.1% (from 6.1% to 8.1%) and by 24.7% among all pluralities from 1990 to 2005 (Martin, Hamilton *et al.*, 2007) (Figure 4).

Preterm delivery can be either spontaneous or medically induced (indicated) regardless of the gestational age at delivery. Spontaneous preterm birth account for 75% of all preterm deliveries (Meis, Ernest *et al.*, 1987; Meis, Goldenberg *et al.*, 1998; Meis, Michielutte *et al.*, 1995) and can be the end result of three main clinical presentations: 1) preterm labor with intact membranes; 2) preterm prelabor rupture of membranes (preterm PROM); and 3) cervical insufficiency. (McElrath, Hecht *et al.*, 2008) Indicated preterm birth results from medical intervention due to maternal or fetal complications that necessitate medical intervention. (Ananth and Vintzileos, 2006b; Mazaki-Tovi, Romero *et al.*, 2007; Meis, Michielutte *et al.*, 1995; Ananth and Vintzileos, 2006a; Ananth, Getahun *et al.*, 2006) Although many studies have focused on the rate of preterm birth, (1999; Joseph, Kramer *et al.*, 1998; Vintzileos, Ananth *et al.*, 2002) an important consideration is whether these deliveries are the result of spontaneous labor or "indicated" preterm deliveries. The need for this distinction is based on the premise that the risk factors for recurrent preterm PROM, preterm labor with intact membranes, preeclampsia, and/or SGA are different. However, recent observations suggest that there may be overlap among these conditions, (Ananth and Vintzileos, 2006a; Ananth, Getahun *et al.*, 2006) so that a patient with an "indicated" preterm birth may also be at risk for spontaneous preterm birth (Ananth and Vintzileos, 2006a; Ananth, Getahun *et al.*, 2006). The converse may also be true (i.e. that a patient with a spontaneous preterm birth is at risk for an "indicated" preterm birth in a subsequent pregnancy).

Assisted reproduction technologies are emerging contributors for the increasing rate of preterm birth. The use of infertility treatments has risen dramatically in the past 20 years; between 1996 and 2003, the number of cycles of ART nearly doubled from 64,681 to 122,872 (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). The number of live births resulting from conceptions achieved by the use of ARTs more than doubled from 14,507 to 35,785. This has been associated with the trend to delay childbearing, indeed, more than 50 percent of these women were 35 years of age or older. In recent years, an unintended consequence of the use of these technologies, multiple gestations and the increased risk for preterm delivery, has become a focus of attention. Indeed, the institute of Medicine in the USA has concluded that "Fertility

treatments are a significant contributor to preterm birth among both multiple and singleton pregnancies." (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007).
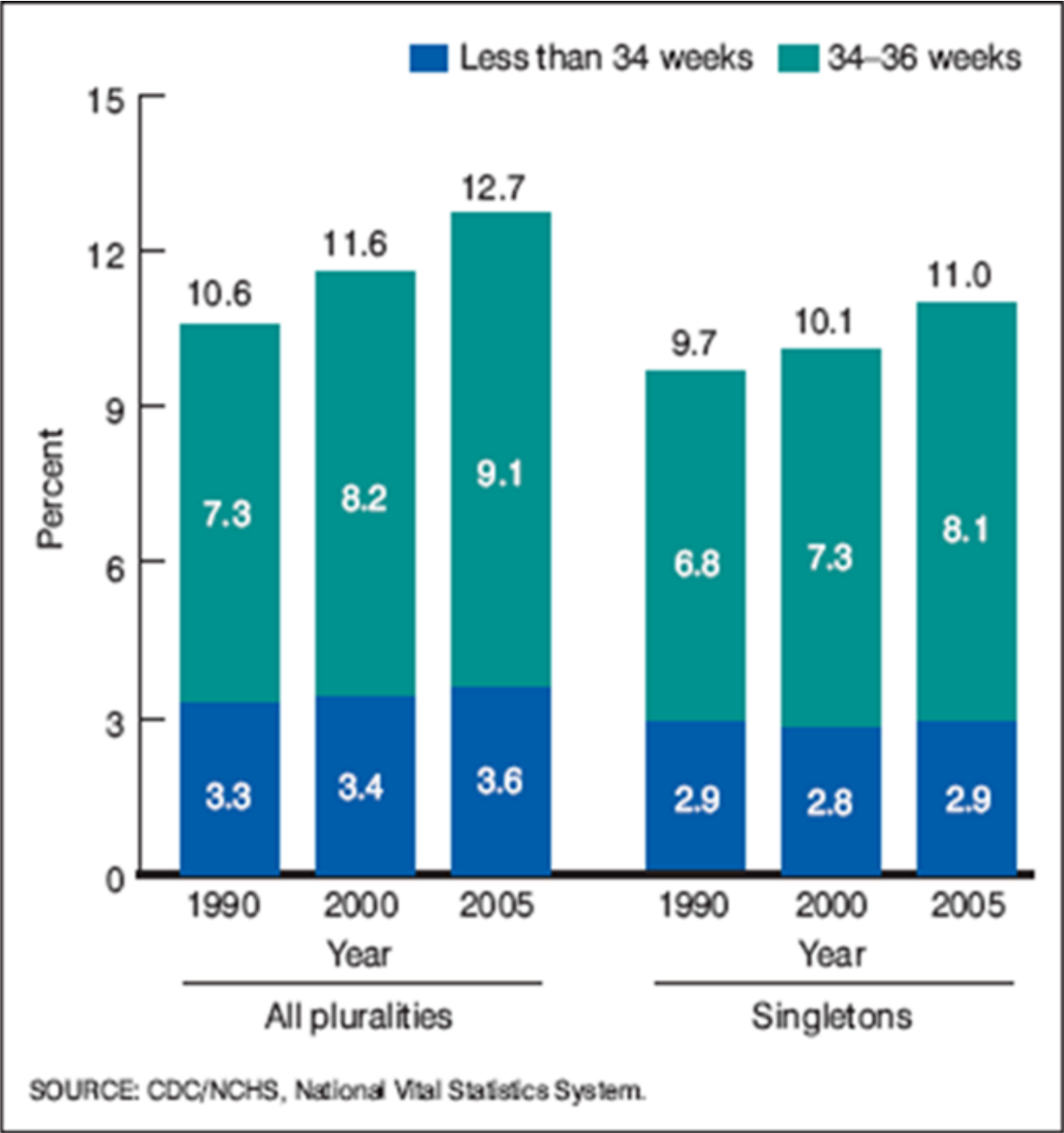

Fig. 4. Chances over time in the rate of preterm birth according to gestational age at delivery and the number of fetuses.

ART are associated with increased rate of pregnancy complication. Several questions are being raised in regard with this topic:1) what are the causes or mechanisms leading for such complications? Is it the treatment or the underlying maternal condition that leads to infertility? 2) Are these complications due to multiple gestation or they affect also singleton gestations? 3) Is there an association with between the ART protocol and adverse pregnancy outcome?

5.1 The association between ART and multiple gestations

There is a direct relationship between the rise in the use of assisted reproduction and the increasing rate of multiple gestations. This trend is mostly due to the transfer of multiple embryos. In spite of the new regulation regarding the maximal embryos transferred during IVF cycle. In 2008, among the ART cycles that used fresh non-donor eggs or frozen-thawed embryos and progressed to the embryo transfer stage, approximately 38% involved the transfer of three or more embryos, about 13% of cycles involved the transfer of four or more embryos, and approximately 4% of cycles involved the transfer of five or more embryos. In addition, ART conceived pregnancies have a higher rate of zygotic splitting in cycles were a single embryo was transferred resulting in increased rate of monochorionic twins than spontaneously conceived pregnancies (Blickstein, Jones *et al.*, 2003; Blickstein, Verhoeven *et al.*, 1999). Among the 38,631 pregnancies that resulted from ART cycles using fresh non-donor eggs or embryos, approximately 61% were singleton, 29% were twins, and about 4% were triplets or more. Approximately 32% of the pregnancies ending in live births produced more than one infant (30% twins and approximately 2% triplets or more). This compares with a multiple-infant birth rate of slightly more than 3% in the general U.S. population Figure 5.
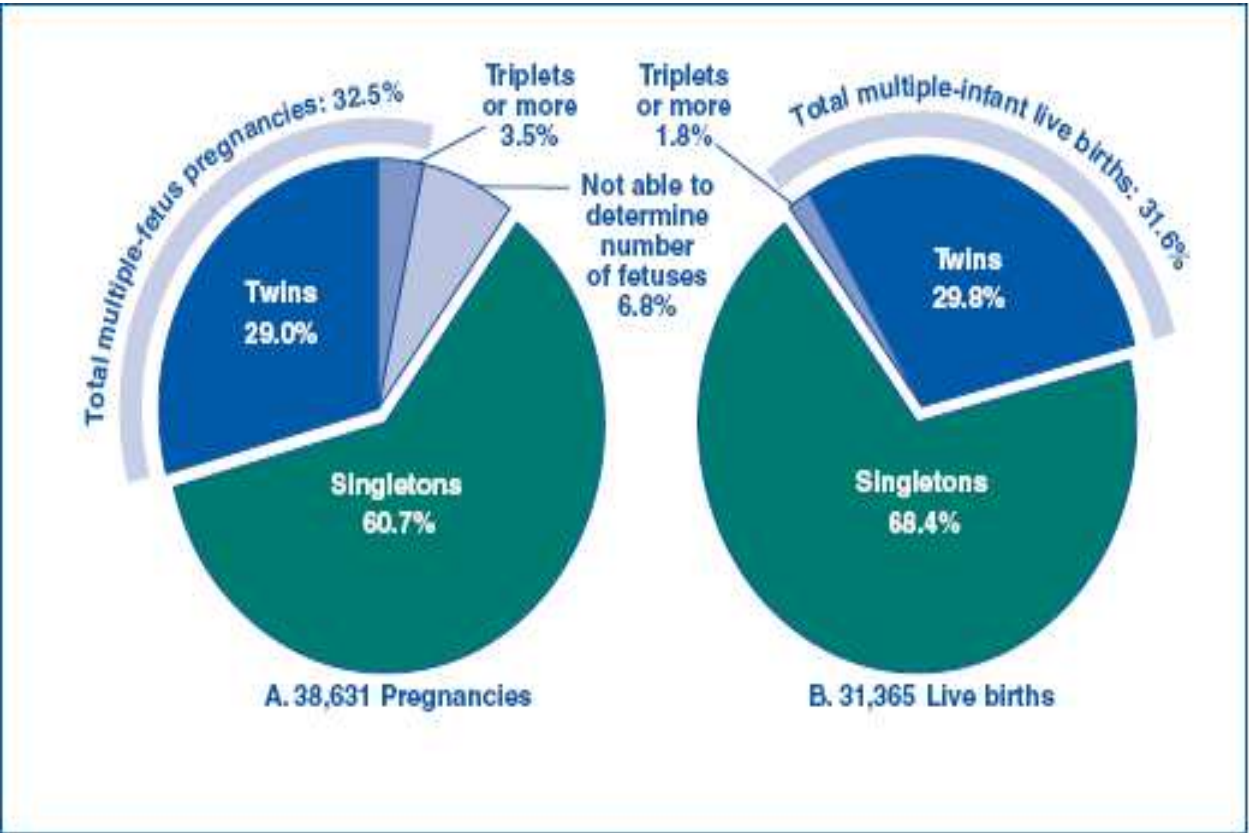

Fig. 5. Risk of having multi-frtus pregnancies and multiple infant live birth from ART cycles using fresh non-donor eggs or embryos-US CDC 2008.

The proportions of multiple birth in Europe is lower than in the USA, and is declining in the recent years. Indeed, the proportion of singleton, twin and triplet deliveries after IVF and ICSI combined was 79.2, 19.9 and 0.9%, respectively. This gives a total multiple delivery rates of 20.8% compared with 21.8% in 2005 and 22.7% in 2004 (ESHRE, 2006). In

an effort to reduce the number of higher-order multiple pregnancies, the American society for reproductive medicine (ASRM) and the Society for Assisted Reproductive Technology Data (SART) have developed guidelines for the number of embryos to be transferred in IVF cycle.

5.1.1 What is the effect of the mode of conception on the risk for preterm birth in twin gestations?

Twin and higher order of multiple gestation are at increased risk to deliver preterm. Nevertheless, the effect of mode of conception on the prematurity rate in twin pregnancies is under continues debate. Several studies have stated that twin pregnancies conceived through ART have similar perinatal complication rate (Zaib-un-Nisa, Ghazal-Aswad *et al.*, 2003; Boulet, Schieve *et al.*, 2008). In contrast, other studies and number of meta-analysis demonstrated no difference between spontaneously and ART conceived twin (Daniel, Ochshorn *et al.*, 2000; Wright, Schieve *et al.*, 2003; Wright, Schieve *et al.*, 2004; Wang, Sullivan *et al.*, 2005; Pinborg, 2005; Allen, Wilson *et al.*, 2006; Reddy, Wapner *et al.*, 2007; Chan, Mannino *et al.*, 2007; A B and M K, 2008; Shebl, Ebner *et al.*, 2009; Hansen, Colvin *et al.*, 2009; Weghofer, Klein *et al.*, 2009; Rossi and D'Addario, 2011; Morcel, Lavoue *et al.*, 2010). Verstraelen et al reported in a population based cohort study, that pregnancies conceived by ART have a persistent increased risk for preterm delivery (Figure 6), even after correction for birth year, maternal age, parity, and for infant sex, caesarean delivery, zygosity, and chorionicity (Verstraelen, Goetgeluk *et al.*, 2005).
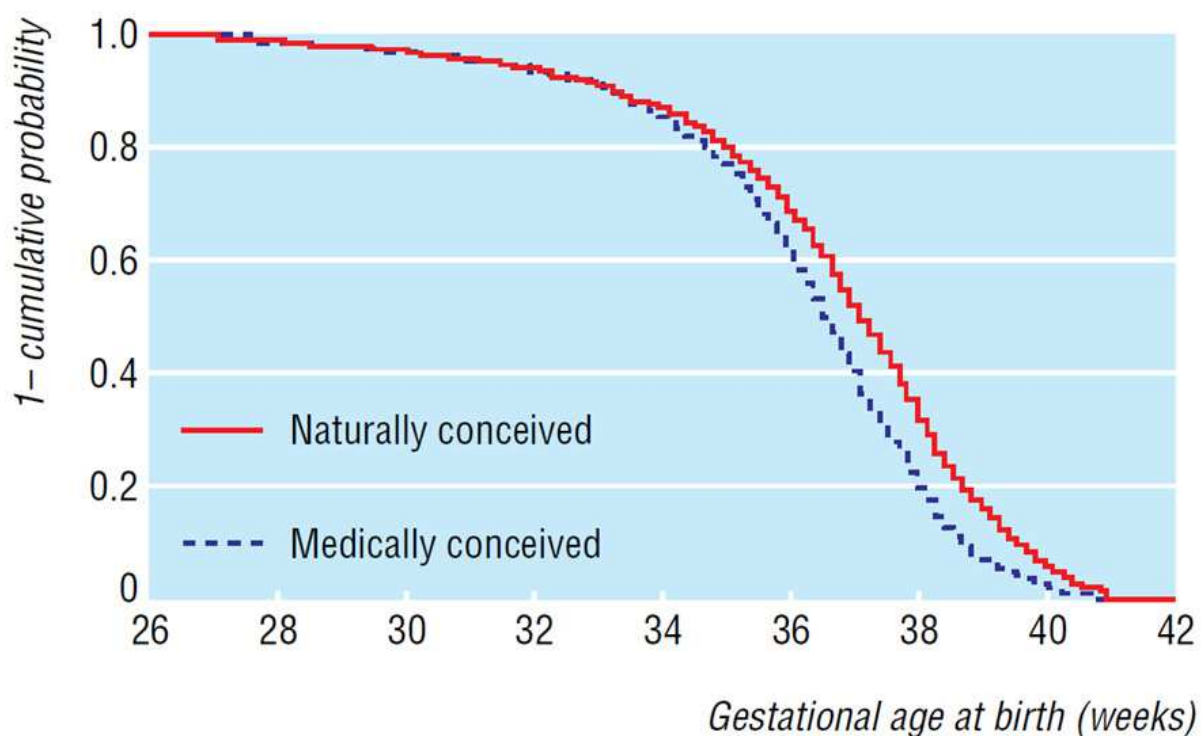

Fig. 6. Kaplan-Meier plot of gestational length in naturally conceived (n=2915) and medically conceived (n=1453) twins. Adopted from Verstraelen H et al. BMJ, 2005; 331: 1173.with permeation.

In addition, Erez et al in a population based cohort study reported that ARTs are an independent risk factor for preterm birth after adjustment to parity, rupture of membranes, severe preeclampsia (Erez, Mayer *et al.*, 2008). In a systematic review and meta-analysis including eleven case-control studies that involved 2303 IVF twins and 2326 spontaneously conceived twins, as well as, three cohort studies that involved at least 1509 IVF twins IVF twins have an increase risk for PTB from 32 to 36 weeks of gestation compared with spontaneously conceived twins who were matched for maternal age (OR, 1.48; 95% CI, 1.05-2.10). The OR for PTB at< 37 weeks of gestation in studies that also matched for parity was similar and approached statistical significance at a 5% level of significance (OR, 1.47; 95% CI, 1.01-2.44). The origin of the increase in PTB has yet to be determined (McDonald, Han *et al.*, 2010). Collectively these studies suggest that in comparison to spontaneously conceived twin gestations, twin pregnancies that result from ART are at increased for preterm birth especially between 32-36 weeks of gestation.

5.2 Are singleton ART pregnancies at increased risk for preterm birth?

One of the major questions regarding the association between ART and preterm birth was whether this effect is mainly due to the increase in the rate of multiple pregnancies or is it relevant also for singleton gestations (Jackson, Gibson *et al.*, 2004; McGovern, Llorens *et al.*, 2004; Schieve, Meikle *et al.*, 2002). Mounting evidence suggest that singleton pregnancies conceived following ART are at increased risk for preterm birth. Indeed: 1) In a Prospective follow-up study done in Denmark, including a total of 20,080 liveborn singletons, in comparison to fertile women, those who conceived following IVF/ICSI had a significant increase in the risk of preterm and very preterm delivery (Wisborg, Ingerslev *et al.*, 2010b). 2) Schieve et al compared the outcome of 62,551 infants born after ART treatments performed in 1996-2000. Secular trends in low birth weight (LBW), very low birth weight (VLBW), preterm delivery, preterm LBW, and term LBW were examined. Detailed analyses were performed for 6,377 infants conceived in 2000. Observed numbers were compared with expected using a reference population from the 2000 U.S. natality file. Singleton infants born after ART in 2000 had elevated risks for all outcomes in comparison with the general population of U.S. singletons: LBW standardized risk ratio 1.62 (95% CI 1.49, 1.75), VLBW 1.79 (95% CI 1.45, 2.12), preterm delivery 1.41 (95% CI 1.32, 1.51), preterm LBW 1.74 (95% CI 1.57, 1.90), and term LBW 1.39 (95% CI 1.19, 1.59) (Schieve, Meikle *et al.*, 2002). 3) In a USA population based surveillance, singletons of mothers who received ART procedures were more likely to be born preterm, with low birthweight, and SGA than singleton infants conceived spontaneously. 4) A meta-analysis revealed that singletons born following IVF are twice as likely to be delivered preterm and die within 1 week of birth compared with the risk of those conceived spontaneously (McGovern et al., 2004). 5) Singletons conceived through the use of IVF are twice as likely to be born preterm and die within 1 week of birth as those not conceived through IVF and 2.7 times more likely to have a low birth weight (Hampton, 2004). 6) A meta-analysis that compiled information from 12,283 singleton births resulting from IVF pregnancies and 1.9 million spontaneously conceived singleton births noted a twofold increase in the risk of preterm delivery (Jackson et al., 2004). 7) According to the CDC report among the infants conceived through the use of ART, singletons that resulted from fetal reduction (either spontaneous or medically) had a higher rate of preterm birth (19%) than those who started as a singleton gestation (12%) (Figure 7).
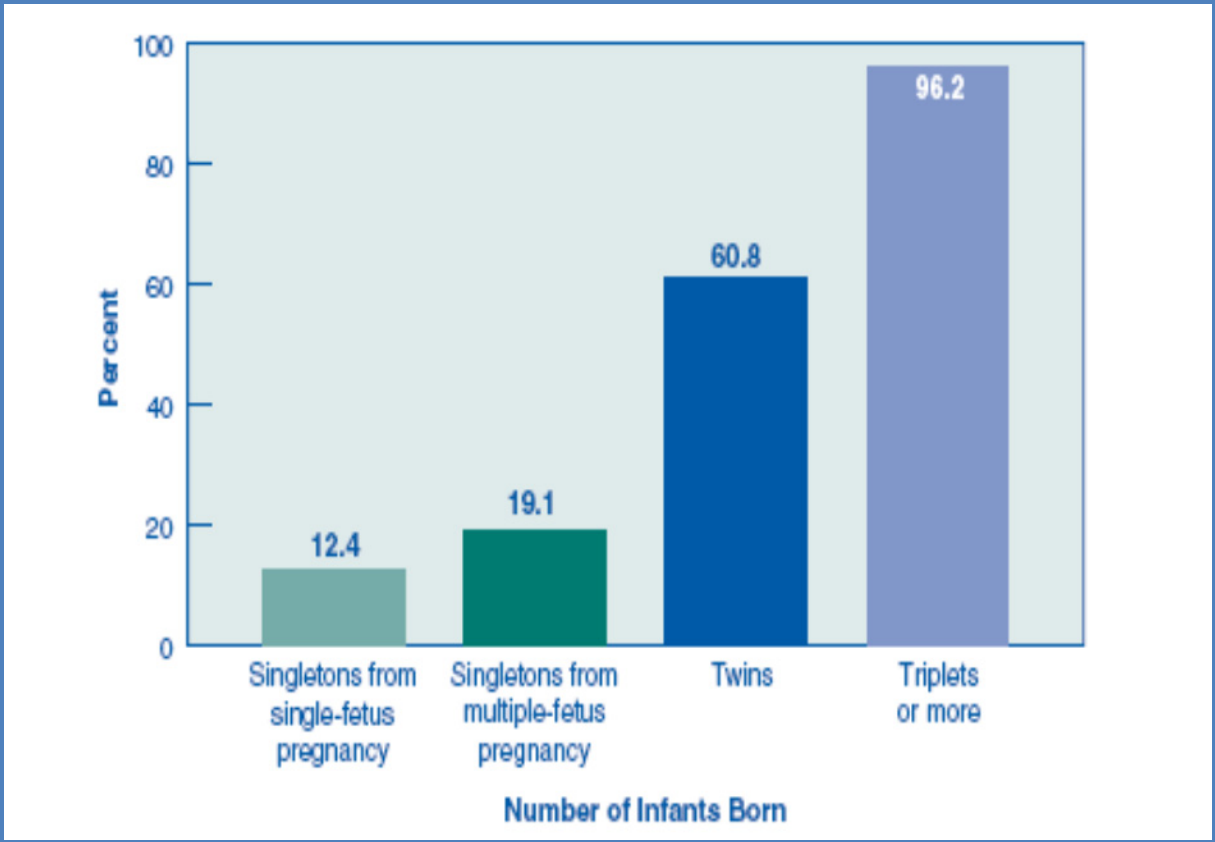
Fig. 7. Proportion of preterm birth resulting from ART cycles using fresh non-donor eggs or embryos, by number of infants born-USA, CDC 2008.

5.3 What are the possible mechanisms associated with the increased risk for preterm birth in ART pregnancies?

The mechanisms in which assisted reproduction technologies increases the risk for preterm birth are still under investigation. Aside the contribution of ART to the increase number of multiple gestations (especially twins) that increases the risk for preterm delivery; the mechanisms leading to preterm delivery in singleton gestation conceived by ART have not been thoroughly investigated yet. Preliminary evidence suggests that underlying maternal conditions that may lead to infertility including insulin resistance and inflammation may contribute to this observation.

5.3.1 Preterm parturition as a syndrome

The implicit paradigm that has governed much of the study of preterm parturition is that term and preterm labor are fundamentally the same process except for the gestational age at which they occur (Romero, Espinoza *et al.*, 2004a; Romero, Espinoza *et al.*, 2006b) and share a 'common pathway'. The common pathway of human parturition is defined as the anatomical, physiological, biochemical, endocrinological, immunological, and clinical events that occur in the mother and/or fetus in both term and preterm labor. The fundamental difference between term and preterm parturition is that the former results from physiological activation of the common pathway, while preterm labor arises from pathological processes that extemporaneously activate one or more of the components of the common pathway of parturition.

Preterm labor (PTL) is the clinical presentation of different underlying mechanisms, (Romero, Espinoza *et al.*, 2004c) including: intrauterine infection, (Romero, Sirtori *et al.*, 1989; Romero, Mazor *et al.*, 1988b; Minkoff, 1983; Goncalves, Chaiworapongsa *et al.*, 2002) uteroplacental ischemia, (Romero, Sepulveda *et al.*, 1993; Combs, Katz *et al.*, 1993; Arias, 1990; Arias, Rodriquez *et al.*, 1993) uterine over-distention, (Hill, Breckle *et al.*, 1987; Phelan, Park *et al.*, 1990; Besinger and Carlson, 1995) cervical disease, (Romero, Mazor *et al.*, 1993; Romero, Espinoza *et al.*, 2006a; Romero, 1996; Heath, Southall *et al.*, 1998; Hassan, Romero *et al.*, 2000) abnormal allograft reaction, (Romero, Sepulveda *et al.*, 1993) allergic phenomena, (Holloway, Warner *et al.*, 2000; Jones, Miles *et al.*, 1996; Rudolph, Reinicke *et al.*, 1993) and endocrine disorders. (Belt, Baldassare *et al.*, 1999; Allport, Pieber *et al.*, 2001) The current taxonomy of disease in obstetrics is based on the clinical presentation of the mother and not on the mechanism of disease responsible for the clinical manifestations. The term 'preterm labor' does not indicate whether the condition is caused by infection, a vascular insult, uterine overdistension, an abnormal allogeneic recognition, stress, or some other pathological process. The same applies to pre-eclampsia, intrauterine growth restriction, fetal death, recurrent abortions, as well as, nausea and vomiting during pregnancy, and failure to progress in labor, in which the diagnoses simply describe the clinical manifestations without consideration of the specific etiology. The lack of recognition that these conditions simply represent a collection of signs and symptoms with little reference to the underlying mechanisms of disease may be responsible for the expectation that one diagnostic test and treatment will detect and cure each of these conditions. This has implications for the fundamental understanding of the biology of preterm parturition and the clinical strategies to diagnose, treat, and prevent spontaneous preterm labour (Romero, Espinoza *et al.*, 2004a; Romero, Espinoza *et al.*, 2006b).

5.3.2 Intrauterine Infection and/or inflammation

Systemic and subclinical infections are a leading cause of preterm birth. Indeed, pyelonephritis and pneumonia are frequently associated with the onset of premature labor and delivery. (Benedetti, Valle *et al.*, 1982; Cunningham, Morris *et al.*, 1973; Fan, Pastorek *et al.*, 1987; Finland and Dublin T.D., 1939; Gilles, Lawson *et al.*, 1969; Herd and Jordan, 1981; Hibbard, Thrupp *et al.*, 1967; Kass, 1962; Madinger, Greenspoon *et al.*, 1989; McLane, 1939; Oxhorn, 1955; Stevenson, Glasko A.J. *et al.*, 1951; Wing and Troppoli D.V., 1930) Similarly, subclinical intrauterine infection is a frequent and important mechanism of disease leading to premature contraction, preterm labor and preterm birth. (Minkoff, 1983; Romero, Mazor *et al.*, 1988a; Bang, 1987; Fidel, Jr., Romero *et al.*, 1994; Kullander, 1977; McDuffie, Jr., Sherman *et al.*, 1992; McKay and Wong, 1963; Rieder and Thomas, 1960; Romero, Munoz *et al.*, 1994; Skarnes and Harper, 1972; Takeda and Tsuchiya I., 1953; Zahl and Bjerknes, 1943; Gomez, Ghezzi *et al.*, 1995; Romero, Sirtori *et al.*, 1989; Goncalves, Chaiworapongsa *et al.*, 2002) Microbiological and histo-pathological studies suggest that infection-related inflammation may account for 25 to 40% of cases of preterm deliveries.

Goncalves et al (Goncalves, Chaiworapongsa *et al.*, 2002) studied the rate of positive amniotic fluid cultures for microorganisms in women with preterm labor and intact membranes. The authors reviewed the results of amniotic fluid cultures from 33 studies and the prevalence of microbial invasion of amniotic fluid among patients with preterm labor was 12.8% (Goncalves, Chaiworapongsa *et al.*, 2002; Romero, Espinoza *et al.*, 2002), and about 50% of them were polymicrobial. The rate of microbial invasion of the amniotic cavity in patients with preterm labor and intact membrane is gestational age dependant. It is as

high as 45% at 23-26 weeks and decreases to 11.5% at 31-34 weeks of gestation (Watts, Krohn *et al.*, 1992). Thus, the earlier the gestational age at preterm birth, the more likely that microbial invasion of the amniotic cavity is present (Watts, Krohn *et al.*, 1992). In preterm PROM, the prevalence of a positive amniotic fluid culture for microorganisms is approximately 32.4%. (Goncalves, Chaiworapongsa *et al.*, 2002; Romero, Espinoza *et al.*, 2002) However, when amniocenteses were performed at the time of the onset of labor, 75% of patients had microbial invasion of the amniotic cavity (Romero, Quintero *et al.*, 1988), suggesting that some patients are already infected prior to the clinical rupture of membranes, while others are infected after the membrane have ruptured. The rate of microbial invasion of amniotic cavity among women presenting with a cervical insufficiency in the mid-trimester is around 33% (range 13%-52%) (Romero, Gonzalez *et al.*, 1992; Bujold, Morency *et al.*, 2008) and 45% to 51% in the early third trimester (Bujold, Morency *et al.*, 2008). In addition, a recent study has demonstrated that while only 8% of patients with cervical insufficiency had a positive amniotic fluid culture, 80% have intra-amniotic inflammation determined by a positive rapid MMP-8 kit (Lee, Romero *et al.*, 2008). Patients with intra-amniotic inflammation and negative amniotic fluid culture had a shorter amniocentesis-to-delivery interval and a lower gestational age at delivery than patients without intra-amniotic infection/inflammation. In twin gestations, microbial invasion of the amniotic cavity occurs in 11.9% of patients presenting with preterm labor and deliver preterm (Romero, Manogue *et al.*, 1989; Romero, Mazor *et al.*, 1988b). The most common microbial organisms isolated from the amniotic fluid of patients with preterm parturition were genital mycoplasmas , *Fusobacterium* species *Streptococcus agalactiae, Petostreptococcus spp., Fusobacterium spp., Staphylococcus aureus, Gardenerella vaginalis, Streptococcus viridans*, and *Bacterioides spp.* (Alanen, 1998; Hitti, Riley *et al.*, 1997; Averbuch, Mazor *et al.*, 1995; Carroll, Papaioannou *et al.*, 1996; Cotton, Hill *et al.*, 1984; Coultrip and Grossman, 1992; Garite, Freeman *et al.*, 1979; Zlatnik, Cruikshank *et al.*, 1984; Romero, Quintero *et al.*, 1988; Romero, Gonzalez *et al.*, 1992)

The association between infection and/or inflammation and preterm birth in ART pregnancies is implied from recently published data. A prospective cohort study that included 144,018 treatment cycles reported that tubal causes of infertility were associated with increased odds of preterm birth (Nelson and Lawlor, 2011). Kamiyama et al (Kamiyama, Teruya *et al.*, 2004) reported that among women undergoing IVF-ET, those who had endotoxin concentrations > 200 pg/mL in menstrual effluent did not conceive, while 30% of those with lower endotoxin concentrations got pregnant. Thus, preexisting endometrial microbial invasion with Gram negative bacteria is associated with failure of IVF-ET, either because of failure of implantation or the induction of sub clinical spontaneous abortion (Romero, Espinoza *et al.*, 2004b). Endotoxin is a component of the cell wall of Gram negative bacteria and its detection in biological fluid is evidence of microbial invasion of a sterile compartment such as the amniotic cavity. An increased concentration in non-sterile body fluids such as cervical mucus or vaginal fluid is an indication of enlarged Gran-negative microbial population and has been reported in women with bacterial vaginosis (Romero, Espinoza *et al.*, 2004b).

5.3.2.1 Bacterial vaginosis and preterm birth

Bacterial vaginosis is a risk factor for spontaneous preterm birth with intact or ruptures membranes (Leitich, Bodner-Adler *et al.*, 2003). The rate of bacterial vaginosis during pregnancy is 15-20%; however, 50% of these patients are asymptomatic. A meta-analysis

(Leitich, Bodner-Adler *et al.*, 2003) of 18 studies (20,232 patients) concluded that bacterial vaginosis was associated with an increased risk for preterm delivery < 37 weeks of gestation (OR 2.19, 95%CI 1.54-3.12), and this effect was significant among singleton gestations, as well as among low and high risk pregnancies for preterm delivery. Detection of bacterial vaginosis <16 weeks of pregnancy was associated with an increased risk for preterm birth (OR 7.55, 95%CI 1.8-31.65) (Leitich, Bodner-Adler *et al.*, 2003). Bacterial vaginosis was also found to be associated with intra-amniotic infection, histologic chorioamnionitis, preterm PROM, first trimester losses in women who conceived after in vitro fertilization, and second trimesters abortions, as well as post cesarean section endometritis and wound infection (Vidaeff and Ramin, 2006; Newton, Piper *et al.*, 1997; Ralph, Rutherford *et al.*, 1999; Llahi-Camp, Rai *et al.*, 1996; Watts, Krohn *et al.*, 1990; Watts, Eschenbach *et al.*, 1989; Chaim, Mazor *et al.*, 1997).

Patients who undergo IVF treatments have a rate of bacterial vaginosis of about 25% (Liversedge, Turner *et al.*, 1999; Wilson, Ralph *et al.*, 2002) which is higher than that observed in other groups of patients (11-15%) (Eschenbach, Gravett *et al.*, 1984; Pavletic, Wolner-Hanssen *et al.*, 1999; Eschenbach, 1993; McGregor, Allen *et al.*, 2001; McGregor and French, 2000; Sobel, 2000; Ugwumadu, 2002). Moreover, bacterial vaginosis was more common among infertile patients with tubal occlusion (Wilson, Ralph *et al.*, 2002), which is independently associated with an increased risk for preterm birth (Nelson and Lawlor, 2011). Bacterial vaginosis was also more common in unovulatory women and those with unexplained infertility than in infertile couples due to male factor or endometriosis (Wilson, Ralph *et al.*, 2002).

Randomized clinical trials for the prevention of preterm birth by antibiotic treatment of patients with bacterial vaginosis have yielded contradictory results (McDonald, O'Loughlin *et al.*, 1997; Kekki, Kurki *et al.*, 2001; Ugwumadu, Manyonda *et al.*, 2003; Guaschino, Ricci *et al.*, 2003; Okun, Gronau *et al.*, 2005; Shennan, Crawshaw *et al.*, 2006; McDonald, Brocklehurst et al., 2005; Carey, Klebanoff *et al.*, 2000). The randomized placebo control trial of the NICHD MFMU network included 1953 women with bacterial vaginosis who were assigned to treatment with oral metronidazol or placebo (Carey, Klebanoff *et al.*, 2000). Treatment with metronidazol was not associated with a significant reduction in the rate of preterm birth. Moreover, a sub-analysis of high risk patients for preterm delivery demonstrated a higher rate of preterm delivery and preterm PROM in the treatment group (Carey, Klebanoff *et al.*, 2000). A Cochrane review concluded that, overall, antibiotic treatment of bacterial vaginosis did not reduce the risk for preterm birth; however, treatment before 20 weeks of gestation may reduce the risk for preterm delivery < 37 weeks (OR 0.72 95%CI 0.55-0.95) (McDonald, Brocklehurst *et al.*, 2007). In conclusion, treatment of bacterial vaginosis before 20 weeks of gestation in patients with a history of previous preterm birth, may reduce the risk for preterm PROM and low birthweight.

5.3.3 Utero-placenta ischemia

Abnormal placentation and vascular lesions in the fetal and maternal sides of the placenta are the second most prevalent lesions observed in patients who deliver preterm (Arias, Rodriquez *et al.*, 1993). Several possible mechanisms can lead to such findings including vaginal and decidual bleeding, spontaneous or iatrogenic death of intrauterine sibling, and uterine vascular changes such as atherosclerosis that are more prevalent in older parturient.

First trimester bleeding among patients with singleton gestation who conceived by ART was associated with an increased risk for: 1) recurrent second-trimester (OR 4.56, 95% CI = 2.76–7.56) and third-trimester bleeding (OR 2.85, 95% CI = 1.42– 5.73); 2) preterm PROM (OR 2.44, 95% CI 1.38–4.31); 3) preterm contractions (OR 2.27, 95% CI 1.48–3.47) as well as increased the risk for preterm birth (OR 1.64, 95%CI = 1.05–2.55) and extreme preterm birth (OR 3.05, 95%CI 1.12–8.31); and 4) NICU admissions (OR 1.75, 95% CI 1.21–2.54) (De Sutter, Bontinck et al., 2006). The origin of vaginal bleeding associated with preterm birth can be either decidual or placental.

Vascular pathology is one of the mechanisms leading to decidual hemorrhage and subsequent preterm birth. Arias et al (Arias, Rodriquez et al., 1993) reported the rate of vascular lesions in placentae of patients with preterm labor was 34% and 35% of those with PROM, in comparison to only in 12% in those of women who delivered at term. The rate of failure of transformation of spiral arteries is higher among patients and preterm labor with intact membranes as well as those with preterm PROM than in patients who delivered at term (Kim, Bujold et al., 2003; Kim, Chaiworapongsa et al., 2002; Romero, Kusanovic et al., 2011; Lockwood, Krikun et al., 2007). Moreover, the changes in the uterine vasculature associated with maternal age contribute as well for the vascular pathology. Indeed, Crawford et al (Crawford, Davis et al., 1997) studied whether uterine artery atherosclerosis is associated with known cardiovascular risk factors in women undergoing hysterectomy. Among the 59 premenopausal women, 55.9% had intimal thickening, 40.7% had simple plaques and 3.7% had complex lesions in the uterine artery samples. Among postmenopausal women, 40% had intimal fibrosis, 20% had simple plaques, and 40% had complex lesions. Postmenopausal status was correlated strongly with the presence of advanced atherosclerotic disease (P < 0.001). Postmenopausal women had significantly greater intimal area (P = 0.01), intimal area/medial area (P = 0.002), intimal area/vessel area (P =0.002), maximal intimal thickness/medial thickness (P = 0.01), and significantly less medial thickness (P <0.001). A significant linear correlation existed between age and the intimal/medial ratio among premenopausal women (P = 0.04) and postmenopausal women (P = 0.01). Patients with electrocardiogram (ECG) abnormalities had significantly greater intimal/medial area as well (P = 0.02). Hypertension was associated with complex lesions among the postmenopausal patients (P = 0.01). Preoperative cholesterol levels greater than 200 mg/dL were associated with greater intimal thickness (P = 0.05) and intimal thickness/medial thickness (P = 0.03) (Crawford, Davis et al., 1997). Moreover, Naeye et al (Naeye, 1983) reported that sclerotic lesions in the myometrial arteries are a possible cause of underperfusion because the proportion of arteries with these lesions increased from 11% at age 17 to 19 years to 83% after the age of 36. This finding is in accord with the report that uterine artery PI during pregnancy increases with maternal age (Pirhonen, Bergersen et al., 2005). These observations are supported also by the clinical findings including an increased rate of SGA neonates among patients with preterm labor and intact membranes as well as those with preterm PROM, and the higher prevalence of low birthweight in ART pregnancies.

Decidual bleeding is thought to play a role in the pathogenesis of preterm labor and preterm PROM leading to preterm birth. Indeed, hemosiderin deposition, that are regarded as a marker for bleeding are found in the decidua and retro-chorionic hematoma formation is present in 37.5% of patients who deliver preterm after PROM between 22 and 32 weeks of gestation, and 36% of patients with preterm delivery and intact membranes (Salafia, Lopez-Zeno et al., 1995). In contrast these lesions are found only in 0.8% of placentas of those who deliver at term.

The effect of decidual bleeding on the activation of premature uterine contractions and/or rupture of membranes is thought to be mediated by thrombin (Lockwood, Krikun et al., 2007; Lockwood, Paidas *et al.*, 2009). The decidua is reach with tissue factor the most potent activator of the coagulation cascade. Thus, any minor decidual bleeding activates the coagulation cascade leading to the generation of thrombin thrombin (Stephenson, Lockwood et al.,2005; Lockwood, Toti *et al.*, 2005; Sarno, Schatz *et al.*, 2006; Lockwood, Krikun et al., 2007). Evidence in support of the increase activation of the coagulation cascade among patients with preterm labor and intact membranes as well as women with preterm PROM include: 1) women with spontaneous preterm labor without intra-amniotic infection or inflammation and women with vaginal bleeding who delivered preterm, have a lower median maternal plasma protein Z (a co factor of protein Z dependent protease inhibitor that inhibits the activity of factor X) than that of normal pregnant women (Kusanovic, Espinoza *et al.*, 2007); 2) regardless to the presence of intra-amniotic infection/inflammation, women with preterm labor and intact membranes have a higher median tissue factor activity and a lower median tissue factor pathway inhibitor than those with a normal pregnancy 3) patients with preterm PROM have a higher median maternal plasma tissue factor concentration and a lower median TFPI concentrations than normal pregnant women (Erez, Espinoza *et al.*, 2008); 4) patients with PTL as well as those with preterm PROM have a higher median maternal plasma thrombin-antithrombin III concentration than that of women with a normal pregnancy (Chaiworapongsa, Espinoza *et al.*, 2002; Elovitz, Baron *et al.*, 2001; Rosen, Kuczynski *et al.*, 2001); and 5) maternal plasma thrombin-antithrombin III complex concentration in the mid trimester were lower in patients about to deliver preterm than in those who subsequently delivered at term (Hackney, Catov *et al.*, 2010).

Moreover, increased thrombin generation was detected not only in the maternal circulation but also in the amniotic fluid (Erez,Romero,et al.,2009). Women with preterm labor who delivered preterm had a higher median thrombin anti-thrombin III concentration than those who delivered at term (Erez, Romer *et al.*, 2009). This was particularly evident among those without intra-amniotic infection/inflammation, in which elevated amniotic fluid of thrombin anti-thrombin complex concentrations were associated with a shorter amniocentesis to delivery interval and a lower gestational age at delivery than those with normal or low concentrations of this complex (Erez,Romero,et al.,2009). A vanishing twin can be an additional possible source for increase intrauterine thrombin generation that may lead to preterm birth. Indeed, vanishing twins among women who conceived by IVF/ICSI was associated with a higher rate of preterm birth <37 and <32 weeks of gestation, especially in the vanishing of the twin occur in later stages of gestation (Pinborg, Lidegaard *et al.*, 2005). A possible explanation for this observation is the report that intrauterine fetal demise is associated with an increased intra-amniotic thrombin generation (Erez, Gotsch *et al.*, 2009). This may be the case also in patients with a vanishing twin, meaning, the increased thrombin generation associated with the dissolving of the dead twin increases the risk for preterm delivery of the surviving fetus.

Thrombin can activate preterm parturition through several mechanisms: 1) it has a uterotonic activity, indeed, the administration of a whole blood into a non-pregnant uterus generated uterine contractions that were not evident when saline or heparinzed blood were introduced into the uterine cavity (Elovitz, Saunders *et al.*, 2000; Elovitz, Baron *et al.*, 2001); 2) thrombin and activated coagulation factor X can induce pro inflammatory cytokines production (IL-6 and IL-1) that may leads to prostaglandins generation and premature myometrial activation and contractions (Lockwood, Toti *et al.*, 2005); and 3) thrombin

activates matrix degrading enzymes such as matrix metalloproteneinases (MMPs) 1, 3 and 9 that can degrade the chorioamniotic membranes leading to rupture of membranes (Rosen, Schatz et al., 2002; Stephenson, Lockwood et al., 2005).

5.3.4 Uterine over-distention

Women with a multiple pregnancy are at increased risk for spontaneous preterm labor and preterm birth. Intra-amniotic pressure remains relatively constant throughout gestation despite the growth of the fetus and placenta. This has been attributed to progressive myometrial relaxation due to the effects of progesterone and endogenous myometrial relaxants such as nitric oxide (Sladek, Westerhausen-Larson et al., 1999). Stretching can, however, induce increased myometrial contractility (Laudanski and Rocki, 1975), prostaglandin release (Kloeck and Jung, 1973), expression of gap junction protein or connexin-43 (Ou, Orsino et al., 1997), and increased oxytocin receptor in pregnant and non-pregnant myometrium (Ou, Chen et al., 1998). The stretch-induced contraction- associated protein gene expression during pregnancy is inhibited by progesterone (Ou, Orsino et al., 1997). The effect of stretch increases in late gestation and is maximal during labor as a consequence of the relative reduction in uterine growth compared with fetal growth and of the declining circulating and/or local concentrations of progesterone (Ticconi and Lye, 2002; Chow and Lye, 1994; Ou, Orsino et al., 1997).

Mechanical stress induces activation of integrin receptors (Tzima, del Pozo et al., 2001), stretch-activated calcium channels (Holm, Rich et al., 2000; Farrugia, Holm et al., 1999), phosphorylation of platelet-derived growth factor receptor (Hu, Bock et al., 1998) and activation of G proteins (Li and Xu, 2000; Hu, Bock et al., 1998). Once mechanical force is sensed, it leads to activation of protein kinase C and mitogen- activated protein kinases, increased gene expression of c-fos and c-jun, and enhanced binding activity of transcription factor activator protein-1 (Shynlova, Oldenhof et al., 2002; Oldenhof, Shynlova et al., 2002; Mitchell and Lye, 2002; Mitchell and Lye, 2001; Piersanti and Lye, 1995; Lefebvre, Piersanti et al., 1995). Other effects of physical forces relevant to myometrium include increased expression of prostaglandin H synthase 2 (Wu, Ma et al., 1999), superoxide dismutase, and nitric oxide synthase. The nature of force/pressure-sensing mechanisms of the myometrium has yet to be determined. A role for integrins and their ligands has been proposed for other organs (Shyy and Chien, 2002; Lee, Millward-Sadler et al., 2002). Stretch may not only induce increased myometrial contractility but may also modify the contractile response through 'mechanoelectrical feedback' similar to the one reported in the heart. The chorioamniotic membranes are distended by 40% at 25–29 weeks of gestation, 60% at 30–34 weeks of gestation, and 70% at term (Millar, Stollberg et al., 2000). Stretching of the membranes in vitro induces histological changes characterized by elongation of the amnion cells and increased production of collagenase activity and IL-8 (Maradny, Kanayama et al., 1996; Maehara, Kanayama et al., 1996), while stretching of amnion cells in culture results in increased production of prostaglandin E2 (Kanayama and Fukamizu, 1989). Recent studies using an in vitro cell culture model for fetal membrane distension revealed upregulation of IL-8 and pre-B-cell colony-enhancing factor (Nemeth, Tashima et al., 2000). When fetal membrane explants were distended in an in vitro distension device to mimic the situation in vivo, and the gene expressions of distended explants were compared with that of nondistended explants, three genes, namely IL enhancer binding factor 2, huntingtin-interacting protein 2, and interferon-stimulated gene encoding a 54 kDa protein, were found to be upregulated (Nemeth, Millar et al., 2000). Collectively, these observations suggest that

mechanical forces associated with uterine overdistension may result in activation of mechanisms leading to membrane rupture.

5.3.5 Insulin resistance

The association between infertility and maternal insulin resistance is well documented and polycystic ovary disease is its classical feature (Lobo, 1995; Barbieri, 1992; Ruutiainen and Seppala, 1991; Franks, Robinson *et al.*, 1996; Davison, 1998; Taylor, 1998; Sills, Perloe *et al.*, 2000; Scarpitta and Sinagra, 2000; Gutmann and Corson, 2001; Nestler, Stovall *et al.*, 2002; Moran and Norman, 2002; Ben-Shlomo, 2003). Indeed, these patients have a higher rate of infertility or sub fertility. The rate of pregnancy complications among patients with polycystic ovary disease is increased and women with PCOS demonstrated a significantly higher risk of developing gestational diabetes [odds ratio (OR) 2.94; 95% CI: 1.70–5.08], gestational hypertension (OR 3.67; 95% CI: 1.98–6.81), pre-eclampsia (OR 3.47; 95% CI: 1.95–6.17) and preterm birth (OR 1.75; 95% CI: 1.16–2.62). Their babies had a significantly higher risk of admission to a neonatal intensive care unit (OR 2.31; 95% CI: 1.25–4.26) and a higher perinatal mortality (OR 3.07; 95% CI: 1.03–9.21), unrelated to multiple births (Boomsma, Eijkemans *et al.*, 2006). Thus these findings suggest that insulin resistance may contribute to preterm birth in twin gestations especially among patients with PCOS. The exact mechanisms leading to preterm birth due to maternal insulin resistance are not clear, recent reports suggest that alteration in adipocytokines may be involved in this process (Mazaki-Tovi, Romero *et al.*, 2008; Mazaki-Tovi, Romero *et al.*, 2009a; Mazaki-Tovi, Romero *et al.*, 2009b; Mazaki-Tovi, Romero *et al.*, 2010; Mittal, Romero *et al.*, 2009).

5.3.6 Endocrine effect of ART

The controlled ovarian hyperstimulation during ART cycles has endocrine implication that may contribute to the increasing rate of preterm birth in these patients. Human Chorionic Gonadotropin (hCG) induces the secretion of relaxin by the corpus luteum (Kristiansson, Svardsudd *et al.*, 1996; Weiss, Goldsmith *et al.*, 1993). Due to the ovarian hyperstimulation during ART cycle the maternal luteal mass is more prominent than that observed during spontaneously conceived pregnancies resulting in the significant increase in relaxin secretion in response to hCG, and indeed, pregnancies following ART were associated with hyper relaxinemia (Kristiansson, Svardsudd *et al.*, 1996; Weiss, Goldsmith *et al.*, 1993). Higher maternal relaxin concentrations were found to be significantly associated with preterm birth (Iams, Goldsmith *et al.*, 2001; Vogel, Salvig *et al.*, 2001; Vogel, Glavind-Kristensen *et al.*, 2002). Relaxin acts by promoting collagenolysis through inducing the activity of matrixmetaloproteinase (MMP) 1-3 and inhibiting tissue inhibitor of metalloprotease-1 (TIMP-1) (Palejwala, Stein *et al.*, 2001); the net effect is remodeling and ripening of the uterine cervix and increased uterotonic activity. Progesterone can counter act relaxin activity by inducing an anti-inflammatory response and decrease the MMP concentrations and uterine contractility (Palejwala, Stein *et al.*, 2001).

6. Prevention of preterm birth

The prevention of preterm birth is one of the major objectives of modern obstetrics. In the US there is an initiative to reduce the rate of preterm birth to 6.1% by 2010, and the March of Dimes has made this topic its main field of interest. In spite of all efforts, at present there is

no specific treatment for spontaneous preterm birth and this is attributed to the syndromic nature of preterm delivery that cannot be resolved by a single medication or intervention. Currently there is wide agreement regarding the beneficial effect of two treatments: (1) the administration of corticosteroids for patients at risk for preterm birth to reduced acute neonatal morbidity; and (2) prophylactic antibiotic treatment for patients with preterm PROM that has occurred from 24 to 32 weeks of gestation (Mercer, Miodovnik *et al.*, 1997; Kenyon, Taylor *et al.*, 2001) but not for preterm labor with intact membranes (Kenyon, Brocklehurst *et al.*, 2008). This treatment has been proven to prolong pregnancy and reduce the rate of acute neonatal morbidity in patients with preterm PROM (Kenyon, Brocklehurst *et al.*, 2008). However, the results of the follow up of children after 7 years were as follows: (1) In children who were born after preterm PROM, neither antibiotic regime was associated with a significant effect on the overall level of behavioral, medical status and academics achievements (Kenyon, Pike *et al.*, 2008). (2) In contrast, prophylactic antibiotic treatment of patients with preterm labor had a negative effect on the children's outcome at the age of 7. Treatment with erythromycin was associated with increased functional impairment of children of mother with preterm labor and intact membranes (Kenyon, Pike *et al.*, 2008). The more worrisome outcome was the higher rate of cerebral palsy among children whose mothers were treated with erythromycin (OR 1.93, 95% CI 1.21–3.09) as well as in those treated with co-amoxicalve (OR 1.69, 95% CI 1.07–2.67) (Kenyon, Pike *et al.*, 2008). Thus, prophylactic antibiotic treatment should not be administrated to patients and preterm labor with intact membranes.

Yet, these treatments are targeted to reduce the rate of complications rather than to prevent the "disease". In the recent years, attempts to prevent spontaneous preterm birth are mainly by two approaches: (1) the administration of progesterone to patients with a history of preterm birth or with a short sonographic cervix; and (2) placement of a cerclage for cervical os insufficiency.

6.1 Progesterone for the prevention of preterm birth

Progestogens administration for the prevention of recurrent abortion or preterm birth has been a subject of investigation (Papiernik-Berkhauer, 1970; LEVINE, 1964; BISHOP, RICHARDS *et al.*, 1950; BISHOP and RICHARDS, 1952; Check, Chase *et al.*, 1987; Tognoni, Ferrario *et al.*, 1980; Gerhard, Gwinner *et al.*, 1987; Johnson, Austin *et al.*, 1975; Hauth, Gilstrap, III *et al.*, 1983; Yemini, Borenstein *et al.*, 1985; Hartikainen-Sorri, Kauppila *et al.*, 1980; Breart, Lanfranchi *et al.*, 1979) and meta-analyses (Daya, 1989; Goldstein, Berrier *et al.*, 1989; Keirse, 1990) or several decades. However, progesterone gained a wide acceptance as a valid treatment for the prevention of preterm birth (2003) only after the publication of the studies by da Fonseca (da Fonseca, Bittar *et al.*, 2003) and the NICHD MFMU (Meis, Klebanoff *et al.*, 2003) who investigated its efficacy in the prevention of preterm birth in women with a history of preterm delivery.

Da Fonseca et al. (da Fonseca, Bittar *et al.*, 2003) reported the results of a randomized, double-blinded, placebo-controlled study including 142 high-risk singleton pregnancies including patients with: (1) at least one previous spontaneous preterm birth; (2) prophylactic cervical cerclage; or (3) a uterine malformation. The patients were randomized to receive either daily vaginal suppository of micronized progesterone (100 mg) or placebo, from 24 to 34 weeks of gestation. The rate of preterm delivery <37 weeks and <34 weeks was lower in the progesterone group than in the placebo group (<37 weeks, progesterone: 13.8% vs.

placebo: 28.5%, *p*=0.03; and < 34 weeks, progesterone: 2.8% vs. 18.6%, *p*=0.002) (da Fonseca, Bittar *et al.*, 2003). The authors concluded that prophylactic vaginal progesterone appeared to reduce the rate of preterm delivery in women at high risk for preterm birth (da Fonseca, Bittar *et al.*, 2003).

The NICHD-MFMU network (Meis, Klebanoff *et al.*, 2003) reported the results of a multicenter double-blind, placebo-controlled clinical trial testing whether 17-hydroxy progesterone caproate (OHPC) administration can reduce the rate of preterm delivery in patients with a history of spontaneous preterm birth. The patients were enrolled at 16 to 20 weeks of gestation and randomly assigned in a 2:1 ratio to receive either a weekly injection of 250 mg of 17-OHPC or a weekly injection of placebo until delivery or 36 weeks of gestation. Treatment with 17-OHPC significantly reduced the rate of preterm delivery at less than 37 weeks, less than 35 weeks, and less than 32 weeks of gestation (<37 weeks, RR 0.66; 95% CI 0.54–0.81; <35 weeks, RR 0.67; 95% CI 0.48–0.93; and <32 weeks, RR 0.58; 95% CI 0.37–0.91]. Moreover, neonates born to women treated with 17-OHPC had significantly lower rates of NEC, IVH and need for supplemental oxygen (Meis, Klebanoff *et al.*, 2003). Thus, among women at high risk for preterm delivery, a weekly injection of 17-OHPC resulted in a reduction in the rate of recurrent preterm birth and several neonatal complications (Meis, Klebanoff *et al.*, 2003). The beneficial effect of 17-OHPC and vaginal progesterone in the reduction of preterm birth and of 17-OHPC in the reduction of the rate of neonates with low birth weight were further supported by systematic reviews meta-analyses and a Cochrane review (Sanchez-Ramos, Kaunitz *et al.*, 2005; Dodd, Crowther *et al.*, 2005; Coomarasamy, Thangaratinam *et al.*, 2006; Mackenzie, Walker *et al.*, 2006; Dodd, Flenady *et al.*, 2006).

In 2007, three new randomized clinical trials on the efficacy of progestogens in preventing preterm birth were reported (Rouse, Caritis *et al.*, 2007; O'Brien, Adair *et al.*, 2007; Fonseca, Celik *et al.*, 2007). The recent randomized clinical trials yielded conflicting results. O'Brien et al (O'Brien, Adair *et al.*, 2007) reported the results of a multinational, randomized, double-blind, placebo-controlled trial of progesterone vaginal gel administration to patients with a history of spontaneous preterm birth between 20 to 35 weeks of gestation. Women were randomized, between 18 to 22 completed weeks of gestation, to receive daily treatment of progesterone vaginal polycarbophil-based gel (Crinone®, 8%, 90 mg) or placebo (Replens®) that were self-administered either until delivery, 37 weeks of gestation, or the occurrence of PROM. Vaginal progesterone did not reduce the rate of preterm birth at ≤32, ≤35, or ≤37 weeks of gestation. Moreover, there were no differences in the neonatal and maternal outcomes (O'Brien, Adair *et al.*, 2007).

The beneficial effect of progesterone in patients with a sonographic short cervix has been recently reported (Facchinetti, Paganelli *et al.*, 2007). A randomized prospective clinical trial (Facchinetti, Paganelli *et al.*, 2007) in which women with preterm labor and intact membranes (25 to 33 6/7 weeks) were allocated to either observation or IM administration of 341 mg of 17-OHPC twice a week until 36 weeks of gestation or delivery was performed. Patients allocated to receive 17-OHPC had a longer sonographic cervical length than those in the observation group (Facchinetti, Paganelli *et al.*, 2007); suggesting that progesterone may have major effects on the uterine cervix.

Fonseca et al. (Fonseca, Celik *et al.*, 2007) reported the results of a randomized clinical trial evaluating the efficacy of vaginal progesterone in reducing the rate of preterm birth in women with a sonographic short cervix (≤15 mm by transvaginal ultrasound between 20 to 25 weeks of gestation). Women were allocated to daily vaginal administration of 200 mg of micronized progesterone or placebo (safflower oil) from 24 to 34 weeks. The frequency of

spontaneous preterm delivery <34 weeks was significantly lower in the progesterone group than that in patients allocated to placebo (19.2% vs. 34.4%; *p*=0.007) (Fonseca, Celik *et al.*, 2007). A secondary analysis of this trial indicated that among women without a history of delivery <34 weeks, the incidence of preterm birth was significantly lower in women receiving progesterone than in those allocated to placebo (RR 0.57, 95% CI 0.35–0.93) suggesting that progesterone may be beneficial to patients with a sonographic short cervix even without a history of preterm birth (Fonseca, Celik *et al.*, 2007).

The secondary retrospective analysis (Defranco, O'Brien *et al.*, 2007) of the study by O'Brien et al (O'Brien, Adair *et al.*, 2007). supports the findings of Fonseca et al (Fonseca, Celik *et al.*, 2007) that patients with a short cervix may benefit from vaginal progesterone administration. However, the authors (Defranco, O'Brien *et al.*, 2007) reported that vaginal progesterone gel may have a beneficial effect in reducing preterm delivery <32 weeks of gestation at a sonographic cervical length of <28 mm (Defranco, O'Brien *et al.*, 2007). These findings imply that the cutoff of 15 mm may be too stringent and progesterone may also work in women with a longer cervix. As the frequency of a cervix of ≤15 mm is 1.7% but that of <28 mm is about 10% (Iams, Goldenberg *et al.*, 1996; Iams, Goldenberg *et al.*, 2001; Iams, Johnson *et al.*, 1995), this could expand the therapeutic range of progesterone.

The study of De Franco et al (Defranco, O'Brien *et al.*, 2007) provides the first hint that vaginal progesterone administration may improve infant outcome in properly selected patients. The frequency of NICU admission was lower in women with a cervical length of ≤30 mm and <28 mm and who had received progesterone treatment than in those allocated to placebo. The same was the case for the duration of NICU length of stay (Defranco, O'Brien *et al.*, 2007). However, these conclusions must be considered tentative because they derive from a secondary analysis which is intended to be hypothesis-generating.

In contrast to the results in singleton gestations, the administration of progesterone for the prevention of preterm birth in twin gestation had no beneficial effect. Hartikainen-Sorri et al (Hartikainen-Sorri, Kauppila *et al.*, 1980) more than twenty-five years ago, and recently Rouse et al (Rouse, Caritis *et al.*, 2007) reported the results of a multicenter, placebo-controlled, double-blind, randomized clinical trials of 17-OHPC for prevention of preterm birth in twin pregnancies. Both studies concluded that there was no beneficial effect of 17-OHPC administration for the prevention of preterm birth in twin gestation.

6.2 The role of cervical cerclage in the prevention of preterm birth

Keeping with the view that cervical insufficiency is a mechanical disorder of the cervix, placement of a cervical stitch (cerclage) has been proposed as a treatment for this disorder. The clinical value of cervical cerclage has been subject of many observational and randomized clinical trials (To, Palaniappan *et al.*, 2002; 1993; Althuisius, Dekker *et al.*, 2002; Althuisius, Dekker *et al.*, 2000; Althuisius, Dekker *et al.*, 2001; Althuisius, Dekker *et al.*, 2003; Lazar, Gueguen *et al.*, 1984; To, Alfirevic *et al.*, 2004) and systematic reviews (Belej-Rak, Okun *et al.*, 2003; Drakeley, Roberts *et al.*, 2003a; Drakeley, Roberts *et al.*, 2003b). Yet controversies still exist regarding the subset of patients who will benefit from cerclage.

The current evidence suggests the following: (1) Women who are at low risk for preterm delivery (by history) and have a sonographic short cervix (≤15 mm) will not benefit from cerclage (To, Alfirevic *et al.*, 2004). (2) The benefit of cerclage in women who have a high risk for preterm birth, both by history and a sonographic short cervix observed during the current pregnancy, is controversial (Berghella, Odibo *et al.*, 2004; Rust, Atlas *et al.*, 2000;

Rust, Atlas *et al.*, 2001; Althuisius, Dekker *et al.*, 2000; Althuisius, Dekker *et al.*, 2001). However, a recent randomize clinical trial conducted by the NICHD MFM network among patients with a prior preterm birth <34 weeks of gestation. Patients with a cervical length <25 mm randomly assigned to cerclage reported a beneficial effect of cerclage (Owen, Hankins *et al.*, 2009). This benefit was highly concentrated in women with very short cervical length (<15 mm) (Owen, Hankins *et al.*, 2009). (3) Among patients at risk for preterm delivery, serial sonographic examinations of the cervix followed by cerclage in those who shortened the cervix is a reasonable alternative to prophylactic placement of cerclage based upon uncontrolled studies (Guzman, Forster *et al.*, 1998; To, Alfirevic *et al.*, 2004; Higgins, Kornman *et al.*, 2004). (4) The role of prophylactic cerclage in high-risk patients without a sonographic short cervix for the prevention of preterm delivery/midtrimester abortion (by history) is unclear (1993; Althuisius, Dekker *et al.*, 2001; Lazar, Gueguen *et al.*, 1984; Odibo, Elkousy *et al.*, 2003; Rush, Isaacs *et al.*, 1984). (5) In one trial, emergency cerclage combined with indomethacin administration appeared to reduce the rate of preterm delivery in patients with the clinical presentation of "cervical insufficiency" (Althuisius, Dekker *et al.*, 2003). This evidence indicates that only patients with the clinical presentation of "acute cervical insufficiency" and those with a previous history consistent with "cervical insufficiency" or spontaneous preterm birth and a progressive shortening of the cervix demonstrated by ultrasound may benefit from cerclage placement (Althuisius, Dekker *et al.*, 2001; Althuisius, Dekker *et al.*, 2003; Berghella, Rafael *et al.*, 2011; Berghella, Keeler *et al.*, 2010; Owen, Hankins *et al.*, 2009). The inflammatory status of the endocervix may be an additional criterion to identify those patients that could benefit from cerclage placement and those for whom this intervention may be harmful. (Sakai, Shiozaki *et al.*, 2006)

6.3 The role of progesterone in primary prevention of preterm birth

A recent study by Hassan et al (Hassan, Romero *et al.*, 2011)raised for the first time the possibility of primary prevention of preterm delivery. The study included patients with a short cervix (cervical length between 10-20 mm) who were randomized at 19-24 weeks to the administration of daily vaginal progesterone gel vs. placebo, regardless to their obstetrical history. 32,091 were screened, of them 733 had a short cervix, and 465 were randomized. Women at the progesterone group had a significant reduction in the rate of preterm birth before 33 weeks of gestation and a significant lower rate of neonatal complications in comparison to those in the placebo group (Hassan, Romero *et al.*, 2011). Thus, cervical length is an effective risk assessment tool for the identification of patients at risk for preterm birth and vaginal progesterone gel can prevent preterm delivery in a significant portion of patients with a short cervix.

7. Summary

Assisted reproduction aids a substantial proportion of women to conceive and deliver, however, these pregnancies are at increased risk for preterm birth. Some of the mechanisms leading to preterm parturition in these patients are inherited from the nature of conception like multiple gestations along with their complications. In addition, especially among singleton gestations, ART are an independent risk factor for preterm delivery and this may result from the underlying mechanisms leading to maternal infertility like infection/inflammation of the genital tract as well as other mechanisms. Thus, women who conceived following ART cycles should be followed and treated as a patient at risk for preterm birth.

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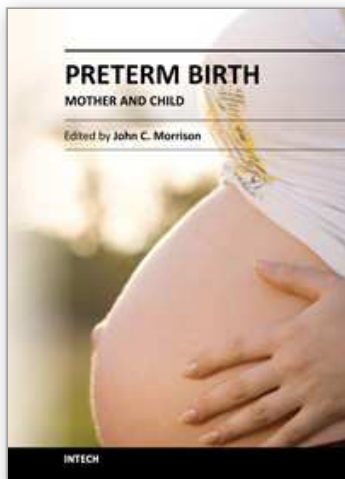
Preterm Birth - Mother and Child

Edited by Dr. John Morrison

While there are many studies and books regarding preterm birth, both the obstetric and in the neonatal/pediatric literature, what is missing is the integration of data from obstetrics through neonatal course and into pediatrics as the neonate transverses childhood. A continued dialogue between specialties is essential in the battle against preterm birth in an attempt to relieve the effects or after-effects of preterm birth. For all of our medical advances to date, preterm birth is still all too common, and its ramifications are significant for hospitals, families and society in general.

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