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Assisted Reproduction and Preterm Birth

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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 et 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., 2008).
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 fertility\n clinic 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).
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)
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=0.018) (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 emphasize that the 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).
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).

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Diabetes per 1,000 live births in specified group</th>
<th>Chronic Hypertension per 1,000 live births in specified group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>44.8</td>
<td>11.0</td>
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<tr>
<td>Under 20 years</td>
<td>14.0</td>
<td>3.9</td>
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<td>20–24 years</td>
<td>25.9</td>
<td>6.4</td>
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<td>25–29 years</td>
<td>42.4</td>
<td>9.9</td>
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<tr>
<td>30–34 years</td>
<td>59.5</td>
<td>13.6</td>
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<tr>
<td>35–39 years</td>
<td>78.6</td>
<td>20.4</td>
</tr>
<tr>
<td>40–54 years</td>
<td>100.5</td>
<td>32.2</td>
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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)
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 a higher risk for fetal death, even after controlling for diabetes, hypertension, and placental abruption (Fretts, Schmittiel 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 influence 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 et 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 complications 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.

![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.](https://www.intechopen.com)

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).
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).
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, Rodriguez 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; Oxhrorn, 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

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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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