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Chapter

Medically Assisted Reproduction and the Risk of Adverse Perinatal Outcomes

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Abstract

Over 5 million children have been born through *in vitro* fertilization (IVF) across the world. IVF is only one of the many methods of assisted reproduction, which can be used to achieve pregnancy in the context of infertility or subfertility. Since the birth of the first IVF child, Louise Brown, in 1978, a number of researchers have started to study the various impacts of the conception through these methods, on both mothers and children. A growing body of evidence suggests that conception through medically assisted reproduction (MAR) is not without risk. Given that MAR is relatively new and that our look back period is short, there is limited evidence on the risks associated to these procedures, both for the mother and the child. In this chapter, we aim to explore the association between MARs and adverse perinatal outcomes specifically. We will first provide you with an overview of the prevalence and trends of use of these methods around the world, and then delve into the associations between MARs and the risk of perinatal outcomes, namely prematurity, being born with low birth weight and/or small for gestational age, and lastly the impact of MARs on cognitive functions including cerebral palsy, behavioral problems, and autism, which are identified later in the child's life.

Keywords: medically assisted reproduction, prematurity, low birth weight, small for gestational age, delay in cognitive function

1. Introduction

1.1 Infertility and subfertility

Infertility is defined as failure to conceive within 12 months of the first pregnancy attempt [1], while subfertility describes any form or grade of reduced fertility [2, 3].

The National Survey of Family Growth interviewed over 12,000 women of childbearing age (15–44 years old) to estimate the prevalence of infertility in the United States (US) [4]. A woman was considered infertile if she reported she and her partner were continuously cohabiting during the previous 12 months or longer, were sexually active each month, had not used contraception, and had not become pregnant [4]. From 1982 to 2006–2010, the percentage of infertile women based on this definition fell from 8.5 to 6.0% [4]. These estimates are lower than the 12–18% incidence of infertility in the US [5]. The frequency of infertility in nulliparous

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women (i.e., primary infertility) increased with age and was reported to be: 7.3–9.1% in women 15–34 years old, 25% in the 35–39 year olds, and 30% in the 40–44 year olds [4].

Infertility and subfertility may be due to conditions originating from the male and/or female reproductive systems [6]. Between 8 and 20% of couples will experience difficulty conceiving [6–9]. Between 1982–1985, the World Health Organization (WHO) performed a multicenter study where they attributed 20% of infertility cases to male factors, 38% to female factors, 27% to causal factors identified in both partners, and 15% could not be attributed to either partner [10]. In the following section, we will provide you with an overview of the main causes of infertility.

1.1.1 Male infertility

A cross-sectional survey of men in the United States aged between 15–44 years showed a prevalence of male infertility of 12% [11]. Male infertility accounts for 19–57% of the identified causes of infertility in couples [9]. In about 30–40% of cases of male infertility, the cause remains unknown [11, 12]. Male infertility can be classified into four main categories which we will briefly describe in the following section.

1.1.1.1 Testicular disease: endocrine and systemic disorders

Testicular diseases including *primary testicular defects* account for 30–40% of male infertility [13]. Primary testicular defects can be further classified into: (1) congenital disorders including Klinefelter syndrome [14] and (2) acquired disorders which can be due to infections (e.g., chlamydia) [15] and smoking [16]. *Hypothalamic pituitary diseases* account for 1–2% for male infertility [13]. Secondary hypogonadism can cause gonadotropin deficiencies, which in turn leads to infertility [13]. Secondary hypogonadism can be (1) congenital [17], (2) acquired (e.g., tumors of the pituitary gland [18]) or (3) systemic (e.g., obesity [19]).

1.1.1.2 Genetic disorders of spermatogenesis

Genetic disorders affecting spermatogenesis can be identified in 10–20% of male infertility cases [13]. With the increasing use of genome-wide association studies, genetic disorders have been linked to male infertility [12, 20]. Specifically, microdeletions and substitutions on the Y chromosome are increasingly recognized as genetic causes of azoospermia (i.e., semen without sperm) and severe oligozoospermia (i.e., semen with a sperm concentration < 15 million sperm/mL compared to the norm of >48 million sperm/mL [20]. Additionally, mutations linked to the X chromosome in men have also been linked to azoospermia [21–23].

1.1.1.3 Posttesticular defects

Posttesticular defects lead to disorders of sperm transport, which account for 10–20% of male infertility cases [13]. The epididymis is an important site for sperm maturation and essential to the sperm transport system. The vas deferens transports sperm from the epididymis to the urethra, where they are diluted by secretions from the seminal vesicles and prostate. Abnormalities at any of these sites, particularly the epididymis and vas deferens, can lead to infertility [13]. The causes of these abnormalities include congenital obstructions of the vas deferens and obstruction following an infection (e.g., chlamydia). Additionally, given that sperm must be ejaculated, any disorder of the ejaculatory ducts can also lead to infertility [13].

1.1.1.4 Idiopathic

In 30–40% of male infertility cases, the cause is classified as idiopathic [13]. In these cases, despite attempting to identify potential mechanisms at play, a cause for abnormal sperm number, morphology, or function cannot be identified [13]. Idiopathic causes should be distinguished from unknown causes which is where men with normal semen analysis and no other identified cause for infertility are unable to impregnate an apparently clinically normal female partner.

1.1.2 Female infertility

In terms of female infertility, the main causes of infertility are ovulatory disorders which account for 21–32%, tubal disorders for 14–26%, while endometriosis is responsible in 5–6% of the cases of infertility [6, 9]. Approximately 30% of couples will have both male and female factors contributing to their infertility [6, 9]. When the cause is identified, a treatment plan can be put in place with the physician. The concern however, is that 8–30% of infertility will remain unexplained, which makes the choice of the course of fertility treatment difficult [24]. In the section below, we have provided you with an overview of the main causes attributed to female infertility.

1.1.2.1 Ovaries

1.1.2.1.1 Ovulatory disorders

Infrequent ovulation (oligoovulation) or absent ovulation (anovulation) results in infertility because an oocyte is not available every month for fertilization. WHO classifies ovulatory disorders into three classes [42]:

- Class 1—Hypogonadotropic hypogonadal anovulation occurs in 5–10% of cases. This would describe women with hypothalamic amenorrhea from excessive exercise or low body weight.

- Class 2—Normogonadotropic normoestrogenic anovulation accounts for 70–85% of cases and includes women with polycystic ovary syndrome (PCOS) and hyper/hypothyroidism.

- Class 3—Hypergonadotropic hypoestrogenic anovulation occurs in 10–30% of cases and characterizes women with premature ovarian failure.

1.1.2.1.2 Oocyte aging

Maternal aging is a known factor of female infertility [25]. The decrease in fecundability with aging could be due to a decline in both the quantity and quality of the oocytes [25, 26].

1.1.2.2 Fallopian tubes

Tubal disease and pelvic adhesions prevent normal transport of the oocyte and sperm through the fallopian tube [27]. The primary cause of tubal factor infertility is pelvic inflammatory disease caused by pathogens such as chlamydia or gonorrhea [28]. Tubal and pelvic adhesions could also be a consequence of endometriosis [27].

1.1.2.3 Uterus

Conditions that distort the uterine cavity can result in implantation failure, which may lead to infertility or recurrent pregnancy loss [29]. The most common malformation, a septate uterus, was associated with pregnancy losses >60% and fetal survival rates of 6–28% [30, 31].

1.1.2.4 Endometriosis

Adhesions within the uterus, the fallopian tubes, and/or the pelvic floor caused by endometriosis could be a cause of infertility [27]. This could be mediated through ovulatory dysfunction, defective implantation, alternations within the oocyte, or impaired fertilization among other hypotheses [32].

1.1.2.5 Obesity

Evidence has demonstrated that obese women are at an increased risk of subfecundity and infertility [33]. It has been shown that the pathway through which obesity could be a precursor to subfertility/infertility may involve a dysregulation in the hypothalamic-pituitary-ovarian axis as well as decreased oocyte quality and endometrial receptivity [33]. Studies have demonstrated a correlation between higher body mass index (BMI) and poor fertility [33].

1.2. Medically assisted reproduction

Fertility treatments are procedures and/or medication interventions used to initiate a pregnancy. MARs include assisted reproductive techniques (ART) as well as ovarian stimulators (OS). In **Figure 1**, we provide you with a visual classification of MAR techniques as a whole, which we have briefly described below.

1.2.1 Assisted reproductive techniques

ART are defined as procedures that include handling of the oocytes and/or sperm, or embryos to generate a pregnancy [1]. ART methods can be categorized as follows:

1.2.1.1 Intrauterine insemination (IUI)

Intrauterine insemination (IUI) is a procedure in which processed and concentrated motile sperm are placed directly into the uterine cavity, and will often be used when the cause of infertility is related to the male [1].

1.2.1.2 In vitro *fertilization (IVF)*

In vitro fertilization (IVF) with or without *in vitro* maturation (IVM) is a cycle of procedures in which oocytes are retrieved from ovarian follicles, fertilized *in vitro* then subsequently the resulting embryo(s) are transferred into the uterus [1]. The number of embryos transferred into the uterus largely depends on the common practice imposed by the country where the procedure is performed. A more recent practice is to perform single embryo transfers (SET). This practice was put in place to decrease the odds of producing multiple embryos per pregnancy. However, through the Canadian ART register's (CARTR) last reports in 2012, it was shown

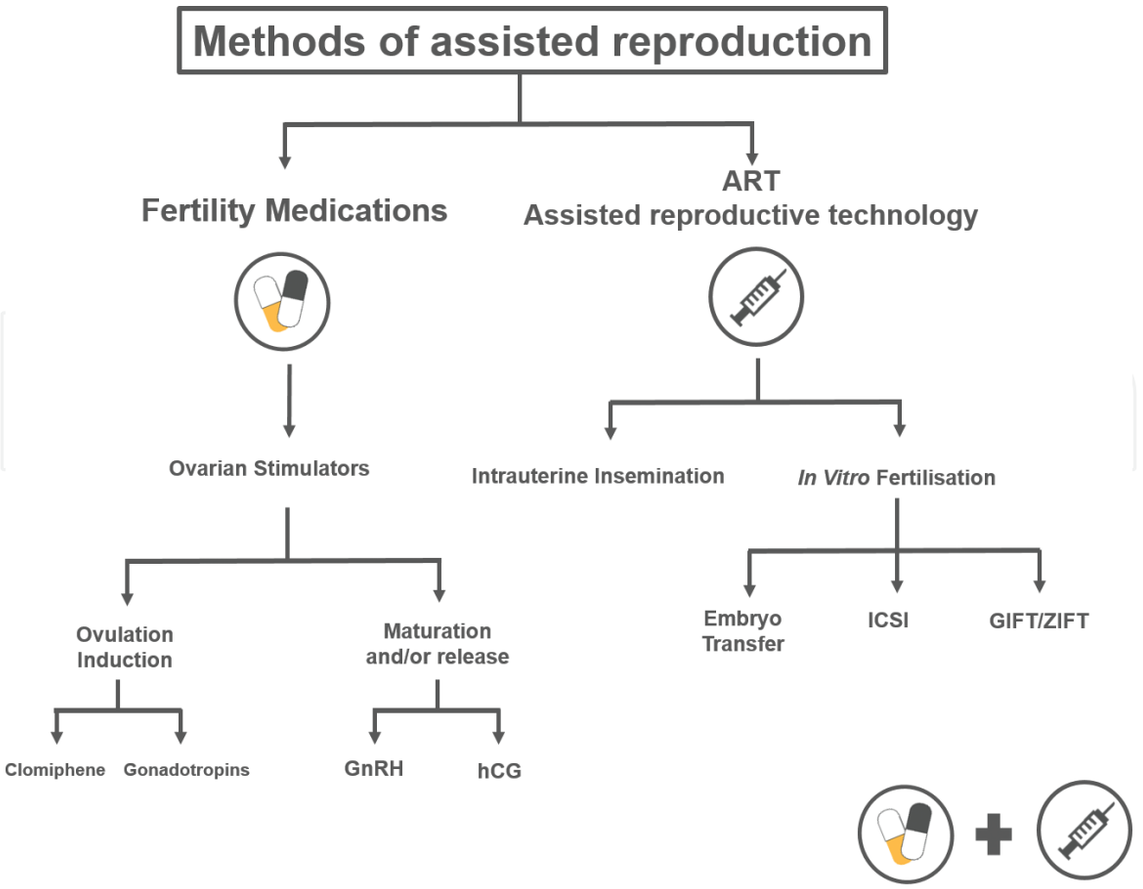

Figure 1.
Overview of the classification of methods of assisted reproduction. Assisted reproductive techniques (ART) are defined as procedures that include handling the oocytes and/or sperm, or embryos to generate a pregnancy (i.e., IVF, ICSI, IUI, in vitro *maturation [IVM], assisted hatching [AH], zygote intrafallopian transfer [ZIFT], gamete IFT [GIFT]), while MAR techniques include ART and OS [1]. Depending on the indication of the use of fertility treatments, women will either be given a course of OS, undergo ART procedures alone or will be subjected to a combination of both OS and ART.*

that SET has yet to become common practice. Australia/New Zealand and Sweden used SET in >70% of the reported ART cycles involving transfers, compared to 44% in Canada and 14% in Germany [34, 35]. These numbers translated into different rates of multiple pregnancy per country: Australia/New Zealand and Sweden had the lowest rates at 6.9% and 5.9%, respectively, while Canada was at 16.5% and Germany had the highest rates of all reported countries at 32.5% [34, 35]. IVF procedures can be categorized as follows:

- Intra cytoplasmic sperm injection (ICSI) is an *in vitro* procedure in which a single spermatozoon is injected into the oocyte cytoplasm [1].

- Assisted hatching (AH) an *in vitro* procedure in which the zona pellucida of an embryo is either thinned or perforated chemically, mechanically or by laser in order to assist the separation of the blastocyst. The blastocyst is the stage that the embryo reaches 5–6 days following fertilization [1].

- Gamete intrafallopian transfer (GIFT) is an *in vitro* procedure in which both gametes (oocyte and sperm) are transferred into the fallopian tube [1].

- Zygote intrafallopian transfer (ZIFT) is an *in vitro* procedure in which the zygote(s) is/are transferred into the fallopian tube [1].

1.2.2 Ovarian stimulators

Ovarian stimulators (OS) are used to promote the development and ovulation of more than one mature follicle among subfertile women mainly to increase the likelihood of conception [36]. This treatment can be used alone or in combination with IUI, wherein we increase the number of oocytes and sperms together. OS can also be used with other ARTs, described above [1, 37]. In many cases, OS will be used as first line therapy when aiming to treat infertility/subfertility in women or couples. OS alone are more likely to be used in the context of unexplained infertility and age-related subfertility in women [36, 38, 39]. Depending on the underlying cause of infertility, different OS may be used. Mainly, OS can be classified as having two roles as they are either used to induce ovulation (i.e., clomiphene, gonadotropins) or to assist with maturation and/or the release of the oocyte (i.e., human chorionic gonadotropin [hCG], gonadotropin-releasing hormone [GnRH]).

1.2.2.1 Ovulation induction

Infrequent or irregular ovulation (i.e., oligoovulation) unrelated to ovarian failure can usually be treated successfully with ovulation induction (OI); women treated with OI agents achieve fecundability nearly equivalent to that of couples not suffering with infertility or subfertility (i.e., 15–25% probability of achieving a pregnancy in one menstrual cycle) [40]. Agents used for OI tend to be used as a first-line treatment to stimulate the development and ovulation of >1 mature oocyte in women with unexplained or age-related subfertility/infertility [36, 39, 41]. OI agents include clomiphene and gonadotropins. **Clomiphene** is a selective estrogen receptor modulator with both estrogen antagonist and agonist effects that increases gonadotropin release [42]. It is known to be effective in women with normal gonadotropin and estrogen levels but who still have ovulatory dysfunction (WHO Class 2) [42]. **Gonadotropins** are used in women with WHO class 2 who have not been able to ovulate using clomiphene or an insulin sensitizing agent such as metformin (used in women with PCOS). This therapy may also be used in women classified as WHO Class 1 [42].

1.2.2.2 Ovulation maturation and release

Agents used for final ovulation maturation and release are known as trigger shots. The gold standard agent to induce follicular maturation has been hCG which mimics the surge of luteinizing hormone that occurs mid-cycle and allows for the release of the oocyte [43]. GnRH may also be used to replace hCG. Current evidence suggests that GnRH may be used as a first-line treatment in egg donors [43].

2. Trends in medically assisted reproduction use

It has been speculated that fecundability has declined over the years, but results need to be replicated at the scale of large populations in order to be confirmed [44, 45]. Nonetheless, the number of women resorting to fertility treatments remains on the rise. As reported by CARTR, the use of ART has increased steadily over the years, having more than tripled in the last decade [34]. From the participating fertility clinics in the CARTR reports over the years (n = 28–32), 16,315 ART cycles had been performed in 2009 compared to 27,356 cycles in 2012 across Canada [34]. In 2012, Canada had the second lowest number of ART cycles after Sweden

(n = 17,628), while the US had the highest number with 176,247 ART cycles performed as reported by the American Society for Reproductive Medicine [34, 35].

Over 5 million children have been born through IVF specifically worldwide [46]. At present, 1–3% of all children in industrialized countries including France, Germany, Italy, Scandinavian countries, and the United States are born through ART [47–49]. Over 1.5 million IVF cycles are performed every year, yielding over 350,000 children annually in Europe, as reported by the European Society of Human Reproduction and Embryology [46].

Between 2010 and 2014, the province of Quebec was the first Canadian province to put in place an assisted reproduction program which provided universal reimbursement for MARs. This program aimed to: (1) reduce multiple pregnancies with the practice of SET, (2) help subfertile/infertile couples to have children, and (3) increase Quebec's birth rate [50]. Following the start of the reimbursement program, reports have shown that MAR represented approximately 2% of all pregnancies [50], of which 43% were from OS without any other ART [51]. Another 20% of women were exposed to OS in combination with IUI, and 33% conceived through IVF [50, 51]. Due to the fact that OS tend to be used the first-line fertility treatment and that it is prescribed with most ARTs, it is the most prevalent exposure [52].

3. Medically assisted reproduction and perinatal outcomes

Since Louise Brown, the first IVF baby, was born in the United Kingdom in 1978, over 5 million children have been born with IVF worldwide [46]. General concerns about the safety of pregnancies resulting from MARs and the health implications of these methods on the resulting child remain, as there is a growing body of evidence supporting the association between these methods and adverse perinatal outcomes [53, 54].

The association between MARs and multiple pregnancies has been studied extensively and is known [51, 55–58]. ART alone and OS use alone have both been associated to increase multiple pregnancies, which occur for two different reasons [57, 59, 60]. On the one hand, ART alone may lead to the transfer of multiple embryos as described above, while on the other hand OS use may lead ovarian hyperstimulation [57, 59–61]. Indeed, ovarian hyperstimulation occurs in more than 40% of stimulated cycles [62]. In the context of ovarian stimulation, it is more difficult to prevent multiple gestations with OS use because it involves the stimulation of ovulation which leads to an unpredictable follicular growth number [61]. As we have described above, the rate of multiple pregnancies associated with ART around the world varies from 5.9 to 32.5% [19, 20]. In a systematic review and meta-analysis performed by Chaabane et al. [63] looking at the association between OS use and multiple pregnancies, they pooled a total of nine studies that had estimates ranging from 1.01 to 50.20 [63]. They calculated a pooled relative risk (RR) of 8.80 with a 95% confidence interval (CI) ranging from 5.09 to 15.20. To put these numbers in context, the rate of multiple pregnancies in the general population is about 3% around the world [64]. These estimates therefore suggest that OS use alone leads to an approximate multiple pregnancy rate of 26% among its' users [46].

ART has also been associated with increased perinatal morbidity and mortality, which the scientific community mainly attributes to the increased risk of multiple births, the use of these technologies themselves, as well as the underlying condition for which these methods are used, which is the infertility factor [54, 65–70]. In fact, it is generally well accepted that multiple pregnancies occurring in the context of fertility treatments due to the transfer of multiple embryos are associated with being born premature (<37 weeks of gestation) or at a low birth weight (LBW;

<2500 g at birth) [71]. These complications, among others, carry long-term impacts on the child, which we will explore throughout this chapter.

Researchers have been making an effort to evaluate adverse risks associated with MARs in singleton babies specifically. In fact, MAR-conceived singletons have been shown to be at increased risk of very preterm (28 to <32 gestational weeks) and moderately preterm birth (32 to <37 gestational weeks), LBW, small for gestational age (SGA; weight below the 10th percentile for their gestational age), neonatal intensive care unit (ICU) admissions (odds ratio [OR], 1.27; 95%CI, 1.16–1.40), and overall perinatal mortality (OR, 1.68; 95%CI, 1.11–2.55) compared to spontaneously conceived singletons [72, 73]. In line with these findings, IVF-conceived children tend to be hospitalized for longer (n = 9.5 days versus 3.6 days in non-IVF children), and use more in-patient care than their non-IVF counterparts in the neonatal period and later in life due to increased risk of asthma, cerebral palsy, congenital malformations, and infections [74]. It could be speculated that these results are due to prematurity or multiplicity, but this observation persisted when restricted to term infants and singletons, respectively [74].

A growing body of evidence suggests that children conceived through ART are phenotypically and biochemically different from naturally conceived children [75]. Indeed, MAR involves hyperstimulation, manipulation, and culture of gametes/embryos at the most vulnerable stage of development [76, 77]. ART has been implied to affect the epigenetic control in early embryogenesis [78, 79]. In fact, MARs have been associated with an increased risk of imprinting disorders both in experimental and epidemiological studies [80, 81]. Furthermore, we must take into consideration the impact of iatrogenic factors including gamete manipulations and ovulation hyperstimulation, as well as the initial underlying cause of infertility as discussed above.

In the following section of the chapter, we will present the associations between MARs and the risks of the main perinatal outcomes (i.e., prematurity, LBW, SGA) as well as long-term cognitive outcomes.

3.1 Prematurity

In the previous section, we discussed the known association between MARs and the risk of multiplicity. Multiplicity has been shown to increase the risk of preterm birth by 6-fold [82]. More recently, efforts have been made by the scientific community to evaluate the contribution of MARs on the risk of prematurity among singletons specifically. As such, we are able to tease out the role of multiplicity in the association between the MARs themselves and the risk of prematurity [83, 84].

Evidence from a systematic review of matched controlled studies showed that MAR-conceived singletons were at an increased risk for very preterm (28 to <32 weeks' gestation) and moderately preterm birth (32 to <37 weeks' gestation), compared to spontaneously conceived singletons [72, 73]. The RRs reported for 13 studies ranged from 0.57 (0.21–1.56) performed among 118 women [85] to 8.00 (1.87–34.2) performed among 240 women [86]. The general consensus among these 13 matched studies was that the risk of preterm birth was doubled [72]. Most studies included in this systematic review adjusted for maternal age and parity by design (i.e., matched case-control studies), but most failed to perform adjustments for confounding variables such as smoking, socio-economic status, and pre-existing chronic conditions [72]. Further supporting these results, ART users were 3.27 times more at risk of prematurity than non-ART users (RR, 3.27; 95%CI, 2.03–5.28). ART was also associated with a doubling of the risk of delivering moderately preterm (RR, 2.05; 95%CI, 1.71–2.47) [87–89]. To put these results in context, the prevalence

of prematurity is of 7.8% in Canada and 10% in the USA [90]. These results indicate that among MAR-conceived children, the prevalence of prematurity could be estimated at 15% or higher.

We found that the current literature does not appropriately take into account the different fertility treatments separately and do not create the necessary distinction between OS and ART [72, 87–89]. MARs are either pooled all together or only IVF or ICSI are considered in analyses. Further studies are required to explore the biological mechanisms through which these methods could cause premature birth/delivery, which will only be possible once we have assessed each MAR distinctively.

3.2 Low birth weight

ART conceptions have been associated with being born LBW. Results have mainly been attributed to higher rates of multiple pregnancies and prematurity among MAR conceptions [91]. Recent meta-analyses have shown that the higher rates of LBW are observed in both IVF singletons as well as twins, respectively, compared to natural conceptions [92, 93]. When comparing singleton ART-conceived children to those who were spontaneously conceived, we observed a 1.70-fold increase in the risk of LBW among ART singletons (RR, 1.70; 95%CI, 1.50–1.92) [72]. In Canada, the prevalence of LBW was of 6.2% in 2013 [94] which is lower than the prevalence reported in the USA in 2016, which was of approximately 8% [95]. To put these numbers into context, this would mean that among ART-conceived children, the prevalence of LBW would be between 11 and 13%. Additionally, when comparing singletons conceived through ART to those who were naturally conceived, the meta-analysis showed a 3-fold increase in the risk of being born very LBW which is defined as a birth weight of <1500 g (RR, 3.00; 95%CI, 2.07–4.36) [72].

A number of studies have shown that IVF-conceived singletons were at an increased risk of being born LBW, even following adjustment for gestational age which is a known confounder [96–102], while two large prospective studies and one matched case-control did not observe any differences following adjustments [85, 103, 104]. Through they did not all adjust for the same variables, the two prospective studies took into account maternal age, gestational age, education, marital status, BMI, intrauterine exposure to smoking/alcohol/coffee as well as the sex of the child, parity, and time since last pregnancy [103, 104].

Aside from the body of evidence examining the association between ART and LBW, the exposure to OS has also been associated with LBW when compared with spontaneous conceptions in conceptions with [68, 105, 106] and without IVF [101, 107].

It has been hypothesized in this context that an alteration in oocyte quality, decreased receptivity of the endometrium or the production of a poor implantation environment may play a role in this observation [101, 107]. These could in part be mediated through the increased levels of estradiol which could impair the implantation process and this hypothesis has been confirmed in animal studies [91].

3.3 Small for gestational age

In the context of infertility treatments, we have discussed the negative implications of OS on the uterine environment. As such, oocyte manipulation as well as hormonal triggers during implantation could be key players in the mother's response to growth factors [107]. In fact, the capacity of the placental system to transfer nutrients to the fetus as well as the condition of the maternal endocrine system will determine, along with genetics, whether or not the fetus will follow an

expectedly normal growth curve during the gestational period [108]. Being born SGA describes newborns who are smaller than the norm for their gestational age established by the average growth curve [109]. It is important to note that definitions of SGA are population-dependent as growth curves differ from one country to another [109].

Limited evidence exists on the association between MARs and SGA. However, when comparing singleton IVF-conceived children to those who were spontaneously conceived, studies observed a 1.4–1.6 fold increase in the risk of SGA among IVF singletons [72, 110, 111]. An additional study published by the United Kingdom government looked at this association and found a significant increased risk of SGA when comparing IVF to spontaneous conception (RR, 1.98; 95%CI, 1.21–3.24) and also when comparing OS use alone to spontaneous conception (RR, 1.71; 95%CI, 1.09–2.69) [112]. In low- to middle income countries, the prevalence of SGA births is of approximately 27% while in industrialized countries, the prevalence ranges around 5–10% [113]. Based on these prevalences, this would indicate that prevalences of SGA among IVF-conceived children could range from 8.5–45%.

Current evidence is suggestive of an association between MARs and conceiving babies that are SGA. Mechanisms leading to growth restriction *in utero* are those discussed above when describing the probable etiology for the increased risk of LBW [91]. Additional large-scale epidemiological studies are required to confirm these results, as well as to generate further hypotheses to be tested in mechanistic animal studies.

3.4 Long-term cognitive outcomes

Environmental factors that come into play in the early stages of embryonic development can interact with the genotype and alter the capacity of the organism to cope with this environment later in life, therefore modulating a child's susceptibility to disease [114, 115]. Evidence suggests that MAR-conceived children are phenotypically and biochemically different from the spontaneously conceived [75]. MAR involves hyperstimulation, manipulation, and culture of gametes/embryos at the most vulnerable stage of development [76, 77]. However, increased risk of neurodevelopmental disorders in MAR-conceived children may be unrelated to the procedure/treatment itself; MAR has been associated with increased risk of multiple gestation [63], which in turn increases the risk of PTB, LBW, and SGA newborns as we have described in detail in previous sections of the chapter [104, 111, 116]. These adverse outcomes are strongly associated with a range of long-term child outcomes, including vision impairment, cerebral palsy (CP), and neurodevelopmental deficits [46, 117–120]. With the current state of the evidence, results support the hypothesis that MARs could be a contributing factor to the recent increase in the prevalence of neurodevelopmental disorders.

3.4.1 Cerebral palsy

CP is the most common motor disability in childhood. Approximately 1 in 323 children (0.3%) has been identified with CP according to estimates from CDC's Autism and Developmental Disabilities Monitoring Network. Population-based studies worldwide report prevalence estimates of CP ranging from 1.5 to more than 4 per 1000 live births or children of a defined age range [121–124].

Very few groups have evaluated the association between MARs and CP. Most available results stem from studies performed within large registries available in the Scandinavian countries, namely Denmark, Finland, and Sweden. In 2009,

Hvidtjørn et al. performed a systematic review and meta-analysis to provide an overview of the results pertaining to this association [125]. A total of nine studies were included in this review [74, 126–133]. They were conscious to separate results by parity (e.g., all children combined, singletons, twins, and triplets) and to isolate estimates that had been adjusted for PTD, as it is a known risk factor for CP [125]. The outcome was defined by appropriate diagnostic codes of the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*. Only two studies used records from rehabilitations centers, one from questionnaires which were later confirmed by discharge registers. All other studies obtained their information on CP diagnoses from hospital discharge registers.

Among studies looking at all children combined, adjusted ORs ranged between 0.88 and 3.7 [74, 126, 127, 129, 132]. The strongest reported association was that of Strömberg et al. with a significant 3.7-fold increased CP risk when comparing IVF to non-IVF children [132]. After adjusting for PTD, the point estimate was reduced to 2.9 but remained significant [132]. Other studies found no significant association when they adjusted for PTD. Among singleton studies, the tendency was towards an increased CP risk among IVF singletons when compared to their non-IVF counterparts [126–128, 132]. The results of the meta-analysis showed an overall significant 1.8-fold increase (OR, 1.82; 95%CI, [1.31–2.52]) in CP when comparing IVF singletons to non-IVF singletons [125].

Among studies including twins and triplets, the ORs were variable and ranged from 0.6 and 1.5, and most results were not significant [126, 127, 130–133]. Despite their large sample sizes, they had a low number of MAR-conceived children with CP, with numbers ranging from 3 to 15. Additionally, studies did not take into account PTD which could potentially be biasing these results [126, 127, 130–133].

Overall, this systematic review of the literature and meta-analysis suggests that there is evidence supporting the implication of MARs, specifically IVF, in the increased risk of CP. To put these results in context, CP remains a rare outcome with a prevalence of 0.3% on average. These results would suggest that among MAR-conceived children, the prevalence of CP could range between 0.6% and 1%. The increased risk of CP among IVF-born children could be in part explained by the known association between IVF and PTD [125]. Indeed, a more recent study published in 2012 indicates that among MAR-conceived children, the risk of neurodevelopmental outcomes, including CP, is more pronounced among those that are born extremely preterm (22–26 weeks' gestation) [134].

3.4.2 Autism

As discussed above, ART-conceived children are phenotypically and biochemically different from naturally conceived children, likely due to the manipulation of gametes and embryos at such a vulnerable stage of development [75–77]. MARs have been associated with an increased risk of imprinting disorders, which in turn can lead to ASD [80, 81]. Studies have shown that ASD risk is 1.5 to 2 times higher among MAR-conceived children compared with their spontaneously conceived counterparts [125, 135–138]. However, these associations were reduced after adjustments for sociodemographic and perinatal variables including multiplicity, PTD, SGA, maternal diabetes, hypertension and preeclampsia, and cesarean deliver. One small case-control study (n = 942) performed in India looked at the association between exposure to OS and the risk of ASD (measured through questionnaires), and identified a 2-fold increased risk of ASD when compared to their spontaneously-conceived counterparts [139]. To put these results in context, the estimated prevalence of ASD has increased over time from 0.05% in the 1960s [140] to 1.46% today in the USA [141] and is reported to be 1.36% in Quebec,

Canada [142]. This would indicate that among IVF-conceived children, the prevalence of ASD could be of approximately 2%.

On the contrary, other groups have yielded reassuring results when considering ASD as an outcome [143, 144]. Overall, findings remain inconsistent as risk estimate ranges are wide and variable across studies [145]. It is important to note that a number of differences among these studies have been identified, and could therefore explain the disparity among results. Specifically, studies were performed in small populations, which makes it especially difficult to study a rare outcome such as ASD [125, 139, 145]. Additionally, ASD definitions were variable across studies, and were often non-specific which could be due to differences in diagnostic criteria. Some studies used questionnaires which are subject to recall bias, while other studies used diagnostic codes through a registry. However, it is also important to note that over the years, diagnostic criteria used to define ASD have changed between versions of the *Diagnostic and Statistical Manual of Mental Disorders* (4th versus 5th editions) [146, 147]. Lastly, we have identified that there is a lack of evidence and consideration of the immediate and long-term effect of OS alone as most studies focused on IVF or MARs in general without including the pharmacological approach [125, 145].

Throughout this chapter, we have seen that MARs increase the risk of multiple gestation, prematurity, being born with LBW, and SGA. As such, the observed increased risk of ASD in MAR-conceived children may be due to reasons unrelated to the procedure or treatment itself. As we know, MAR has been associated with increased risk for multiple gestations [63], which in turn increase the risk for prematurity, LBW, and SGA babies [104, 111, 116]. We know that these are major risk factors for neurodevelopmental deficits, including ASD [46, 117]. The main question that remains is how MAR techniques contribute to the increased ASD risk. The identified limitations as well as the inconsistency of results underline the importance to produce more evidence on this association by including all exposures to MARs as identified through this chapter.

3.4.3 Behavioral problems

Most studies presented herein measured behavioral problems through a questionnaire which included a Strengths and Difficulties Questionnaire (SDQ). The SDQ is a validated tool comprised of 25 items which aims to assess the psychological adjustment of children and youths [148]. Based on this questionnaire, behavioral problems were defined as having emotional symptoms, hyperactivity, conduct problems, prosocial behavior, and problems with their peers [148]. Depending on the study group, the mother, the teacher or the child themselves (i.e., later as an adult) had filled out the questionnaire to assess the outcome.

The rationale for the evaluation of this association is that couples who undergo a long waiting time before being able to conceive and/or who have had to undergo lengthy fertility treatments tend to experience significant amounts of stress and anxiety during the process. Studies have shown that this increased period of stress may affect their ability to adapt to their new parenting role, which in consequence may influence their children's behavioral and emotional development [149–151]. Animal studies suggest that this response may be largely due to the activity of the stress-responsive hypothalamic-pituitary-adrenal axis and its end-product, which is cortisol [151]. Higher levels of cortisol in the mother during the pregnancy are translated into higher levels in the offspring, which in turn can influence the child's behavior [151]. Further supporting this theory, studies found that women who suffered with symptoms of anxiety late in their pregnancy (32+ weeks' gestation) had higher levels of cortisol in their blood following adjustments for

sociodemographic status, gestational age, parity, and lifestyle factors (i.e., smoking and alcohol consumption) [152, 153].

At both 5 and 7 years of age, the mean behavioral difficulties score was significantly higher in the ART-children when compared to children born through spontaneous conception, even after adjusting for other confounding variables [154]. Indeed, a study performed in the Millenium Cohort comprised of 18,552 women, ART-conceived children had double the risk of having children with peer problems at 5 years of age (OR, 2.56; 95%CI, 1.14–5.77—model adjusted for maternal age, age of the child, sex of the child, household socioeconomic status, family type, maternal qualifications) [154]. A weaker association was observed at age 7 and was non-significant. It was also shown that at the age of 5, ART-conceived children seem to have increased emotional difficulties when compared to those who were spontaneously conceived (adjusted OR, 1.80; 95%CI, 0.86, 3.79). Additionally at age 7, increased peer problems remained (adjusted OR, 1.90; 95%CI, 0.90, 3.98) [154]. Studies have shown that children conceived spontaneously, whether or not mothers/couples struggled with infertility, had similar behavioral patterns [155–159]. These results therefore suggest that the underlying cause of infertility in the parents is unlikely related to resulting behavioral patters in children [159].

To put these results in context, it is estimated that 1 in 10 individuals (10%) will suffer with behavioral problems throughout their life [160]. These results suggest that among MAR-conceived children, the prevalence of behavioral problems could be estimated at 20%.

On the contrary, other studies performed among ART-conceived children did not exhibit any more behavioral problems than their naturally conceived counterparts [125, 155–158]. Some of these studies, unlike the others we have presented, even suggested a more positive relationship between parents and ART-conceived children [159, 161, 162]. Contrary to the previous theory about higher levels of stress among these parents, these results are explained by the fact that ART-conceived children may have a higher desirability factor than their spontaneously conceived counterparts (i.e., planned and unplanned) [159].

Despite the differences in observed results, there seems to be a trend towards an implication of MARs in the development of behavioral problems later in life. The current evidence on behavioral problems suggests that there is a need for the development of long-term surveillance programs (i.e., registries and databases) for MAR-conceived children as of the age of 5 and until early adulthood.

4. Conclusions

The prevalence of MAR use around the world has been increased over the last years. With a noticeable surge of infertility/subfertility among women of childbearing age, these numbers are expected to remain on the rise. Through this chapter, we evaluated the current state of the literature and showed that MARs have been associated with a number of significant adverse perinatal outcomes, which have repercussions on the child later in life, but also on their parents, and society. MAR-conceived children seem to have poorer health overall with increased healthcare utilization largely due to an increased prevalence of prematurity, being born LBW or SGA, and later in life, being more at risk for behavioral problems, cerebral palsy, and autism among other neurodevelopmental outcomes. Decision makers as well as healthcare professionals should be aware of the repercussions that these methods could have on the mother as well as the child, and appropriately inform mothers and couples seeking these therapies to achieve pregnancy in the context of infertility. Further

stufies are needed to present more evidence to strenghten the findings related to perinatal outcomes when conceiving through MARs.

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Conflict of interest

JG and AB have no conflicts of interest to report.

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