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Frauengesundheit in der Praxis

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Well-being of children born after medically assisted reproduction

Abstract

Background: The increasing number and proportion of children born after medically assisted reproduction (MAR) has raised concerns and motivated research about the impact of MAR on the well-being and development of children.
Objective: We summarize existing studies on the well-being and development of children conceived through MAR.
Materials and methods: Review of existing studies.
Results: Children conceived through MAR are at increased risk of adverse birth outcomes such as low birthweight and preterm delivery compared to naturally conceived children. The higher rates of multiple births amongst MAR-conceived children continue to represent an important driving factor behind these disparities. Reassuringly, elective single embryo transfer (eSET)—which is associated with more favourable pregnancy outcomes among MAR-conceived children—is becoming more common. Despite the early life health disadvantages, the evidence on later life outcomes such as physical, cognitive and psychosocial development is generally reassuring. On average, MAR-conceived children show similar or better outcomes than naturally conceived children. The selected and advantaged socioeconomic characteristics of parents who conceive through MAR are likely to play an important role in explaining why, on average, MAR-conceived children perform better than naturally conceived children—particularly in terms of cognitive outcomes. In contrast, there is some evidence pointing to potentially increased risks of mental health problems among MAR-conceived children.
Conclusion: There is need for continued monitoring and longer follow-up studies on the well-being of these children in order to better understand whether their outcomes are similar to or different from those of naturally conceived children, and, if so, why.

Keywords
Assisted reproductive technology · Child well-being · Birth outcomes · Health · Cognitive development

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Zusammenfassung

Kindeswohl nach medizinisch assistierter Reproduktion

Hintergrund: Die steigende Anzahl und der zunehmende Anteil von Kindern, die nach einer medizinisch unterstützten Reproduktion (MAR) geboren werden, haben Bedenken aufkommen lassen und die Forschung zu den Auswirkungen einer MAR auf das Kindeswohl und die Entwicklung motiviert.
Zielsetzung: Wir fassen bestehende Studien über das Kindeswohl und die Entwicklung von Kindern, die durch MAR gezeugt wurden, zusammen.
Material und Methoden: Übersichtsarbeit zu bestehenden Studien.
Ergebnisse: Durch MAR gezeugte Kinder haben im Vergleich zu nichtassistiert gezeugten Kindern ein erhöhtes Risiko für ungünstige Geburtsergebnisse, wie niedriges Geburtsgewicht und Frühgeburt. Ein wichtiger Faktor für diese Ungleichheiten sind nach wie vor die höheren Raten an Mehrlingsgeburten bei MAR-gezeugten Kindern. Erfreulicherweise wird der elektive Einzelembryotransfer (eSET) – der mit günstigerem Schwangerschafts-Outcome nach MAR in Verbindung gebracht wird – immer häufiger durchgeführt. Trotz der gesundheitlichen Nachteile im frühen Lebensalter ist die Evidenzlage zum Outcome im späteren Leben, etwa zur körperlichen, kognitiven und psychosozialen Entwicklung, insgesamt beruhigend. Im Durchschnitt zeigen MAR-gezeugte Kinder ähnliche bzw. bessere Ergebnisse als nichtassistiert gezeugte Kinder. Wahrscheinlich spielen spezifische und begünstigte sozioökonomische Merkmale der Eltern, die durch MAR Eltern geworden sind, eine erheblich Rolle bei der Frage, warum durch MAR gezeugte Kinder im Durchschnitt bessere Leistungen erzielen als nichtassistiert gezeugte Kinder – vor allem hinsichtlich kognitiver Kompetenzen. Andererseits könnten die Anhaltspunkte, die auf möglicherweise erhöhte Risiken für psychische Probleme bei MAR-gezeugten Kindern hinweisen, Anlass zur Sorge geben.
Schlussfolgerung: Es besteht Bedarf an fortgesetzter Beobachtung und längeren Nachfolgestudien zum Wohlergehen dieser Kinder, um besser zu verstehen, ob ihre Entwicklung mit denen nichtassistiert gezeugter Kinder vergleichbar ist oder sich unterscheidet, und, wenn ja, warum.

Schlüsselwörter
Verfahren der assistierten Reproduktion · Kindeswohl · Geburtliches Outcome · Gesundheit · Kognitive Entwicklung

Introduction

The number and proportion of children conceived through medically assisted reproduction (MAR) has been increasing steadily over the last decades [1]. To date, over 9 million births have involved the use of MAR [2]. In 2016, the proportion of children conceived through MAR was between 2–6% in many European countries, with Denmark recording the highest percentage at 9% [1, 3, 4]. These trends have raised concerns and motivated research about the impact of MAR on the well-being and development of children.

Birth/early life outcomes

It is well-established in the medical literature that children born after MAR have worse birth outcomes (e.g. low birth weight and prematurity), and are at higher risk of congenital abnormalities and of rare imprinting disorders (e.g. Prader-Willi and Angelman syndrome) than children who are conceived naturally [5–8]. Although most of the existing evidence focuses on the outcomes of children born after in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI), similar disparities have been documented for children conceived through less invasive MAR treatments, such as ovulation induction and artificial insemination [8, 9]. There are likely to be multiple causes behind the association between MAR treatments and adverse birth outcomes. First, the association is related to the 10–20 times higher rate of multiple births pregnancies associated with the use of MAR than in the general population. It is well-established that there is a higher incidence of poorer birth outcomes in multiple than for singleton births. However, prior studies show that the risk of poorer outcomes is higher for singletons conceived through MAR than for singletons conceived spontaneously [7, 10] which suggests that multiple births are not the only factor contributing to the worse perinatal outcomes of MAR-conceived children. Second, the association could be related to parental characteristics that predispose the parents to use MAR to conceive, and to have a high risk of adverse birth outcomes. For example, prior research shows that subfertility is a risk factor for adverse birth outcomes and is likely to be integral to the MAR-adverse outcome association [11]. Third, the association could be related to the sociodemographic characteristics of the parents and/or children. It is well-established that MAR-conceived children are more likely to be born to older parents and to be the firstborn [12]—factors that have been linked to increased risk of poorer birth outcomes [13, 14]. Conversely, the advantaged socioeconomic profile that typically characterizes MAR families [12]—which is protective against the risk of adverse birth outcomes [15]—might mask some of the underlying risk associated with the MAR techniques.

Accounting for multiple births, subfertility and demographic characteristics attenuate but do not fully explain the association between MAR and adverse birth outcomes. Researchers, practitioners and prospective MAR patients alike are interested in how much of the residual effect should be attributed to the MAR treatments per se such as the freezing and thawing of embryos, the delayed fertilisation of the oocytes, the hormonal treatments or the culture media composition [16]. To address this question, a few studies have attempted to isolate the effects of MAR treatments from other characteristics by applying a sibling design to large-scale population register data [17–20].

A sibling design approach involves comparing birth outcomes of children conceived naturally and through MAR within the same family, which enable the researchers to account for all parental characteristics—some of which are often unobserved in the data (e.g. subfertility, genetic factors, underlying health, socioeconomic factors)—shared by siblings. These studies found a substantial decrease in the magnitude of the negative effects of MAR treatments once accounting for all (unobserved) parental characteristics shared by siblings, suggesting that the role of the MAR procedures per se on birth outcomes is likely to be negligible. One of the studies [17] also highlighted that, after accounting for the higher rates of multiple births in MAR pregnancies and socioeconomic characteristics, the effect of MAR is substantively smaller than the effect of other risk factors. For example, the effect of being the first-born rather than the second- or third-born was, respectively,

three and four times higher than the effect of MAR. The effect of smoking during pregnancy was three times higher.

MAR-conceived children face a higher risk of adverse birth outcomes, but it seems to be largely due to factors other than the treatments per se. Conversely, the persistently higher rates of multiple births amongst MAR-conceived children continue to represent an important driving factor behind the disparities in birth outcomes amongst MAR and naturally conceived children. However, reassuringly, the rates of multiple births in MAR pregnancies have been declining over time—in Nordic countries particularly—because of the introduction of elective single embryo transfer (eSET) policies [3]. As a result, recently born cohorts of MAR-conceived children show improved birth outcomes [21]. A wider utilization of eSET will contribute to further lower rates of adverse birth outcomes amongst MAR-conceived children and to make it a less pressing issue in the future.

Outcomes in childhood and adolescence

In contrast to the large body of evidence that points to a link between MAR and adverse birth outcomes, evidence on the longer-term well-being of children born after MAR is less developed and conclusive.

The existing findings on *physical health* generally suggest that children born after MAR appear to be healthy and to be growing similarly to naturally conceived children [22–25]. The evidence on the overall risk of cancers is reassuring, although the evidence on specific cancers is still limited [16]. A subset of studies have found an increased risk of childhood illnesses, including asthma [26], and a 20% increased risk of hospital admission during the first 5 years of life [27–29]. Moreover, there is some evidence to suggest that children born after MAR may be at increased risk of metabolic and cardiovascular diseases [30–33]. The causality is still unclear. Furthermore the role of the MAR treatments and of other factors associated with MAR conception in explaining these associations is not established.

The findings on *mental health* are mixed. Some studies argue that MAR-conceived children face a higher risk of mental health problems [30, 34–37], whilst others have not documented differences [38–41]. A similar picture has emerged during the adolescent period with some studies not finding an association [37, 40–42], whilst others have documented increased risks of depression or socioemotional problems [34]. The mixed results may be due to methodological limitations as several studies have relied on small or nonrepresentative samples. Differences in methodological approaches could also play a role, as some studies only show adjusted results, and other studies fail to adjust for potential confounders [37]. Recent studies by Rissanen et al. [43] and Barbuscia et al. [42] have highlighted the importance of showing results before and after adjustment for parental characteristics. MAR-conceived children followed up to young adulthood showed a moderately higher risk of psychiatric disorders and psychosocial problems only after adjustment for confounding by family characteristics. There is need of more systematic evidence to understand whether there is a link between MAR conception and offspring mental health, and if so, why.

The literature on *neurodevelopmental outcomes* shows that neurological sequelae, such as cerebral palsy, are more frequent in children born after MAR than in their spontaneously conceived counterparts [44]. These disparities have been largely attributed to the higher frequency of twin pregnancy, low birth weight, and prematurity in the MAR subgroup. The overwhelming majority of studies on (full-term) MAR children have shown that in childhood, they have neurodevelopmental outcomes similar to those of naturally conceived children [45, 46]; however longer follow-ups are needed as very few studies have been conducted looking at adolescents [31].

In relation to cognitive outcomes such as *cognitive abilities and education*, the evidence is reassuring since most studies document no substantial differences between MAR and naturally conceived children. Most studies report that, on average, MAR-conceived children outperform naturally conceived children before adjustment for parental characteristics [12, 47–50]. The advantage is explained by the above-average socioeconomic status of parents who undergo MAR treatments [51]. In fact, after adjustment for confounding by parental social background, the association is attenuated and in some studies even reverses, although the disadvantage is substantively small [49]. MAR-conceived children, on average, perform better not because of their mode of conception, but rather because MAR conception is associated with higher than average socioeconomic status. Whilst the evidence is reassuring, only a few studies have examined academic achievements in adolescents.

As further reassurance, a recent study by Cozzani et al. [52] shows that despite the higher rates of adverse birth outcomes amongst MAR than naturally conceived children, the former do not experience any disadvantage in their cognitive development in childhood and adolescence. MAR-conceived children who are born low birth weight (LBW) do not show any disadvantage in cognitive development compared with naturally conceived children who are born normal weight. It appears that the advantaged socioeconomic profile of families who conceive through MAR plays a crucial role in attenuating the effect of being born LBW which prior literature shows to be associated with worse cognitive development [15]. Despite the considerably higher rates of LBW, MAR-conceived children have better or similar cognitive outcomes than naturally conceived children. However, more evidence and longer follow-ups are needed.

Conclusion

Compared to naturally conceived children, children conceived through MAR are at increased risk of adverse birth outcomes such as low birthweight, preterm delivery and birth defects. Despite the early life health disadvantage, the evidence on physical development in childhood, cognitive and psychosocial development is reassuring. On average, MAR-conceived children show similar or better outcomes than naturally conceived children. However, some studies show increased risks of mental health disorders amongst MAR children and adolescents. Overall, more evidence is needed before we can reach conclusions on the longer-term well-being of MAR-conceived children.

Parents conceiving through MAR tend to be selected: they are older at the time of birth, more likely to give birth to their first child and to be socioeconomically more advantaged than parents who conceive naturally [51]. The selection is explained by the fact that in many contexts access to the treatments is not subsidized, but also because of (e.g. cultural, geographical and religious) barriers to access. The selection into MAR is important to consider when analysing the outcomes of MAR-conceived children. Older parental age and primiparity are associated with worse birth outcomes [53, 54], but also with higher cognitive development and education. Higher parental socioeconomic status is an important predictor of higher educational attainment [55], and to some extent fewer mental disorders and psychosocial problems [56]. Although on the one hand MAR-conceived children's characteristics could point to lower levels of psychosocial problems, the MAR conception process may be associated with stress and mental health problems [57], which could affect children's psychosocial development [42]. However, prior studies show better parent–child relationships and higher closeness in families who have conceived through MAR to families who have conceived naturally [40, 57] which could compensate for the increased levels of stress during the pregnancy seeking process and early life years.

MAR is a complex variable which reflects a range of biological, demographic, socioeconomic and psychosocial processes. As a result, there could be important trade-offs integral to the MAR/child well-being association which could explain some of the inconsistencies documented by existing studies in whether and how MAR is associated with well-being. Whereas on the one hand MAR children have worse birth outcomes, on the other, adults who conceive through MAR treatments are a selected subpopulation group whose advantaged characteristics could compensate for any early life disadvantage. Yet, the MAR process could expose them to stress and mental health problems which persist over time. As a result, MAR children could have worse, similar, or better outcomes depending on the dimension of well-being under consideration, and whether the dimension is more likely to be affected by health (e.g. birth outcomes, physical/mental health) or by social processes (e.g. educational outcomes). Longitudinal studies which analyse several dimensions of well-being before and after adjustment for parental sociodemographic and psychosocial characteristics will be beneficial in elucidating the association between MAR and offspring well-being, as well as in clarifying the causality and the underlying mechanisms.

Given that the number and proportion of MAR-conceived children born increases every year, there is need for continued monitoring and longer follow-up studies on the well-being of these children in order to better understand whether their outcomes are similar to or different from those of naturally conceived children, and, if so, why.

Practical conclusion

- **Children conceived via MAR (medically assisted reproduction) face higher risks of adverse birth outcomes (e.g. low birth weight) than children conceived naturally. The increased risks are attributed to a range of factors: the higher rates multiple births in the MAR group, the subfertility of couples who conceive via MAR and their demographic profiles as they tend to be older at the time of birth and more likely to give birth to their first child (both risk factors for adverse birth outcomes) than couples who conceive naturally. Whilst recent studies suggest that the role of the MAR techniques on birth outcomes is likely to be negligible, the rates of poorer birth outcomes amongst MAR-conceived children continue to be a concern. A wider utilization of eSET (elective single embryo transfer) will contribute to further lower rates of adverse birth outcomes amongst MAR-conceived children and to make it a less pressing issue in the future.**
- **The overall evidence on later life outcomes is reassuring. MAR children appear to have similar or better (physical, cognitive and educational) outcomes than children conceived naturally. A potential cause of concern is that some studies show increased risk of mental health problems amongst MAR-conceived children but the underlying (psychosocial, demographic or biological) mechanisms are still unclear. Systematic evidence is needed on the longer-term well-being of MAR-conceived children.**

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