



Original article

# Longitudinal growth of French singleton children born after in vitro fertilization and intracytoplasmic sperm injection. Body mass index up to 5 years of age

*Croissance anthropométrique d'enfants singletons nés après fécondation in vitro avec ou sans micro-injection intracytoplasmique d'un spermatozoïde. Évolution de l'indice de masse corporelle jusqu'à l'âge de 5 ans*

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Received 5 September 2015; accepted 25 January 2016

Available online 6 April 2017

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## Abstract

**Background.** – The literature presents conflicting results on the epigenetic effect of in vitro fertilization (IVF) on the short-term and mid-term growth of children. These contradictory results may be related to the use of heterogeneous methodologies and non-longitudinal data. The goal of this study was to compare the body mass index (BMI) of children conceived via IVF and spontaneous conception (SC) children, using longitudinal data from birth to 5 years.

**Methods.** – This study compared 118 singleton children born after in vitro fertilization, with or without intracytoplasmic sperm injection (ICSI), selected from a pre-existing single-center cohort to 320 SC children from the same geographic area. BMI and its evolution were analyzed using the mixed-effect model during three periods: before standing acquisition (from birth to 1 year of age), during standing acquisition, and the following period from 2 to 5 years of age.

**Results.** – BMI means were not significantly different between groups regardless of the period, when adjusting for confounding factors related to parents, pregnancy, and children's characteristics and lifestyle. Nevertheless, during the standing acquisition period, children born after IVF-ICSI presented a less significant decrease in BMI ( $P < 0.05$ ). In addition, for each period we identified influencing factors (maternal BMI, level of wealth indicator) associated with BMI.

**Conclusion.** – In the study population, the suspected epigenetic influence of IVF reported in the literature was not observed for BMI from birth to 5 years of age. Further investigations need to be conducted to determine if the suspected influence of IVF on adiposity could be expressed through other parameters.

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**Keywords:** In vitro fertilization; Intracytoplasmic sperm injection; Children; Growth; Body mass index; Follow-up

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## Résumé

**Position du problème.** – Des résultats contradictoires sont retrouvés dans la littérature concernant l'effet épigénétique de la fécondation in vitro (FIV) sur la santé des enfants à court ou moyen terme et notamment sur leur croissance anthropométrique. Ces contradictions seraient liées à l'hétérogénéité des méthodologies utilisées dans les différentes études ou à l'inadéquation de certaines méthodologies pour l'exploration des données anthropométriques, par exemple l'absence d'un traitement longitudinal de ces données. Notre objectif était de comparer l'indice de masse corporelle (IMC) d'enfants conçus après FIV à celui d'enfants conçus spontanément (CS), en utilisant des données longitudinales de la naissance à l'âge de 5 ans.

**Méthodes.** – Cette étude a comparé 118 enfants singletons nés après FIV, avec ou sans micro-injection intracytoplasmique d'un spermatozoïde (ICSI), sélectionnés parmi une cohorte monocentrique, à un groupe de 320 enfants CS, issus d'écoles primaires situées dans la même zone géographique. L'IMC et son évolution ont été analysés sur trois périodes distinctes : avant l'acquisition de la station debout (de la naissance à l'âge d'un an), durant l'acquisition de la station debout et durant la période suivante (entre l'âge de 2 ans et 5 ans).

**Résultats.** – Pour les trois périodes, après ajustement sur les facteurs de confusions l'IMC moyen des enfants n'était pas significativement différent selon la méthode de conception. Ces facteurs correspondaient à des paramètres parentaux et de grossesse, à des caractéristiques de santé des enfants et à des indicateurs de mode de vie. Cependant entre l'âge de un an et deux ans, les enfants nés de FIV ICSI ont présenté une décroissance de l'IMC significativement plus faible que les autres groupes FIV classique et CS ( $p < 0,05$ ). À chaque période d'âge, l'analyse a identifié des facteurs d'influence différents sur l'IMC de l'enfant.

**Conclusion.** – Dans la population étudiée, l'effet épigénétique de la FIV sur la croissance de l'enfant, suspecté dans la littérature, n'a pas été observé sur l'IMC jusqu'à l'âge de 5 ans. D'autres investigations méritent d'être conduites afin de déterminer si d'autres paramètres adipeux pourraient refléter cet effet suspecté.

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**Mots clés :** Fécondation in vitro ; Injection intracytoplasmique de spermatozoïdes ; Enfants ; Croissance ; Indice de masse corporelle ; Suivi longitudinal

## 1. Introduction

Assisted reproductive technologies (ART) are known to adversely affect perinatal outcomes, increasing the risks of preterm delivery, along with the frequency of low birth weight and neonatal morbidity [1,2]. For this reason, health outcomes (such as cardiometabolic health as well as psychomotor and psychological development) are currently being investigated in the context of children born of either conventional in vitro fertilization (IVF) or IVF with intracytoplasmic sperm injection (ICSI) [3–7].

In animal models, manipulation of both gametes and in vitro embryo culture have been shown to induce epigenetic disorders in growth and development genes [1].

In ART children, imprinted diseases are more frequently caused by epimutation in genes controlling the expression of growth, whereas in spontaneous conception (SC) children, genetic disorders are more frequently found to be responsible for such pathologies. Although a link between in vitro manipulation and DNA methylation differences is suspected, the clinical outcome in humans has not yet been demonstrated [8–10]. Recently, some authors found that the culture duration and culture media influence early embryo development [10,11]. Indeed, a higher birthweight is observed in singletons born after blastocyst transfer than in those born after the 3rd-day transfer. Moreover, culture media is associated with fetal overgrowth [11].

A recent review of the literature [1] suggests that epigenetic changes, likely to occur when using ART and to compromise the environment of the embryo, may affect children's development, especially cardiovascular development [1].

Anthropometric measures and adiposity, considered as indicators of cardiovascular development [1,12–14], can be

used as an epigenetic alteration marker. The most widely studied variables are weight, height, body mass index (BMI), and insulin-like growth factor (IGF-I or -II) levels [1–4].

At birth, some authors describe significantly lower birth weight in ART vs SC children [12,13,15–17], while others found no birth weight difference [18–21]. Moreover, these results remain contradictory at later ages since some studies report similar height, weight, and IGF-I levels for 3-year-old [6,22–24] and 5-year-old children [18,19,21]. Other studies note differences in some anthropometrical indicators such as increased height and IGF-II blood levels at 4 and 10 years of age [14,25], lower weight for the first 2 [26] or 3 [22] years of life, and a lower BMI for 5.5-year-old children in the ICSI vs SC groups [20].

These long-term follow-up studies do not consider data as longitudinal or do not always explore the usual confounding factors (such as maternal overweight or obesity, maternal educational level, socioeconomic status, or children's lifestyle). Methodological choices may explain these contradictory results.

Consequently, we compared BMI progression between IVF, ICSI, and SC children, during their first 5 years of life using longitudinal data and adjusting for the usual confounding factors in childhood growth surveys.

## 2. Materials and methods

### 2.1. Set-up and study population

Three groups of children were selected: the children in the first group were conceived after conventional IVF and called the IVF group, the second group after IVF with intracytoplasmic sperm injection (ICSI) and called the ICSI group, and

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