

RESEARCH ARTICLE

Clinical implications of first-trimester ultrasound dating in singleton pregnancies obtained through *in vitro* fertilization

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Data Availability Statement: All relevant data are within the paper and its [Supporting Information](#) files.

Abstract

Background

In pregnancies obtained by in-vitro fertilization (IVF) the exact day of conception is known. For that reason, IVF pregnancies are currently dated according to the day of oocytes retrieval and consequent embryo transfer. The aim of the present study is to determine whether the knowledge of the exact day of conception in IVF pregnancies is a sufficient argument against dating these pregnancies by first trimester ultrasound measurement of the crown-rump length (CRL), as it is recommended in natural conceptions.

Methods

A retrospective study was performed, including all women with singleton pregnancies conceived by IVF who underwent the first-trimester ultrasound scan for the screening of aneuploidies between January 2014 and June 2019. For each pregnancy GA was determined using two alternative methods: one based on the date of embryo transfer (GA_{IVF}), and one based on ultrasound measurement of CRL (GA_{US}). GA were compared to search for any discrepancy. The impact of pregnancy dating on obstetric outcome was evaluated.

Results

Overall, 249 women were included. Comparing GA_{US} and GA_{IVF} , a median difference of 1 [0 – 2] days emerged ($p < 0.001$), with GA_{US} being in advance compared to GA_{IVF} . This discrepancy persisted when subgroups were analyzed comparing different IVF procedures (conventional IVF versus ICSI, cleavage versus blastocyst transfer, frozen versus fresh transfer). No impact of the dating method on obstetric outcomes was observed, being no differences in the rate of preterm birth or abnormal fetal growth.

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Conclusions

In IVF pregnancies GA_{US} and GA_{IVF} are not overlapping, since GA_{US} is mildly greater than GA_{IVF} . This could be due to an anticipated ovulation and fertilization in IVF pregnancy, rather than an accelerated embryo development. For that reason, it would be appropriate to date IVF pregnancies according to GA_{US} , despite a known date of conception, to re-align IVF pregnancies to natural ones.

Introduction

An accurate estimation of gestational age (GA) is essential to provide an adequate obstetrical management. All the decisive choices taken in obstetric care are based on the correct estimation of GA and small changes in the calculation of the estimated date of delivery (EDD) can influence the distribution and incidence of crucial obstetrics complications, such as preterm delivery or small for gestational age (SGA) newborns.

In pregnancies conceived by in vitro fertilization (IVF), GA is probably the closest possible to the real one, because the precise day of conception is known. IVF pregnancies can be dated on the basis of the day of oocyte retrieval and subsequent embryo transfer [1]. This may be valid also for frozen embryo transfers. Nevertheless, there are still some uncertainties regarding GA estimation in IVF pregnancies. Some of the main concerns are related to the possible time delay between conception and implantation, to the early *in-vitro* embryo development, and, moreover, to the maternal environment, which can be assumed to be extremely different in IVF pregnancies compared to spontaneous conceptions, due to the background infertility condition and the altered hormonal milieu. Data regarding first-trimester fetal development in IVF pregnancies are conflicting [2] and both underestimation and overestimation of the true GA were reported when traditional charts were used for ultrasound pregnancy dating [3–7].

Moreover, IVF pregnancies are known to be associated with a higher risk of adverse perinatal outcomes, which lead to higher incidences of preterm birth, low birthweight and small for gestational age (SGA). This could be due to the higher maternal age, the lower parity, the underlying infertility condition, the higher rate of iatrogenic interventions or the IVF procedure itself [8–11]. Of relevance here is that the methods used for pregnancy dating may also play a role.

The purpose of the present study was to compare GA estimation through the two different methods of pregnancy dating (ultrasound measurement versus calculation based on the time of embryo transfer) in a large population of IVF pregnancies and to assess the impact of pregnancy dating on some obstetric outcomes, such as preterm deliveries, SGA and large for gestational age (LGA).

Materials and methods

All women who had conceived by IVF and who underwent antenatal care at the Department of Obstetrics and Gynecology 'L. Mangiagalli', Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, between January 2014 and June 2019, were retrospectively reviewed.

Only women with singleton pregnancies conceived by conventional IVF or intracytoplasmic sperm injection (ICSI) who underwent first trimester combined screening for fetal trisomies were included. Exclusion criteria were as follows: multiple pregnancy (defined as the evidence of more than one gestational sac at the first ultrasound scan), abnormal karyotype

and/or congenital malformations detected either in pre- or postnatal period. The study was approved by the local Ethical Committee (Comitato Etico Milano area B n. 2955). An informed consent to participate was not required since data were retrospectively analyzed anonymously.

Maternal demographic and obstetric characteristics (including maternal age, race, height, weight, smoking status, and medical history), and ultrasound findings were obtained from the locally used software (*Astraia software gmbh Occamstr. 20, 80802 Munich, Germany*) and from the patients' clinical charts. Data on obstetric outcomes were collected from hospital maternity records.

All selected women underwent first trimester ultrasound scan within 11⁺⁰–13⁺⁶ weeks of GA for the screening of major chromosomal abnormalities. The first trimester combined screening test was scheduled on the basis of the GA determined by the attending gynaecologist, according to the first ultrasound scan performed during pregnancy. At first trimester ultrasound scan gestational age was then reassessed according to the Fetal Medicine Foundation criteria. When these criteria were not met, the examination was rescheduled at a proper GA.

All ultrasound examinations were carried out by experienced and certified sonographers (certification of the Fetal Medicine Foundation, London, UK), using Voluson E8 Expert (GE Medical Systems, Milwaukee, WI, USA) ultrasound equipment.

For each pregnancy, GA was determined using two alternative methods: one based on the date of IVF procedures—oocytes retrieval and embryo transfer (GA_{IVF}) and one based on ultrasound measurement of the fetal crown-rump (CRL) according to standard recommendations (GA_{US}) [12,13].

GA_{IVF} was established according to the following modalities: in fresh cycles the date of oocytes retrieval was considered as the date of conception; in frozen-thawed cycles, the date of conception corresponded to 4 days before the transfer of a cleavage stage embryo or 6 days before the transfer of a blastocyst.

GA_{US} was determined as follows: a midline sagittal section of the whole fetus oriented horizontally and with the genital tubercle in view was obtained and the maximum distance was measured between the head and the rump of the fetus, as a straight line obtained by placing ultrasound calipers at the outer edges of fetal extremities. According to standard recommendations, three measurements were taken, with the average considered as the final measurement [12,13]. GA_{US} was then calculated from CRL through the equation developed by Loughna et al.: $GA = 8.052 * (CRL * 1.037)^{1/2} + 23.73$ [14]. Both GA_{IVF} and GA_{US} were finally converted into menstrual age by adding 14 days.

Women were managed on the basis of GA_{IVF}, according to current clinical practice. Term pregnancies were those ending in a delivery after 37 completed weeks (≥ 259 days), according to the standard definition by the World Health Organization (WHO). Infants were considered preterm when born before 259 days [15]. Induction of labor was performed in pregnancy at or beyond 287 days according to local management practices.

For all newborns, at a given gestational age, the birthweight percentile was calculated using BW charts obtained by the equation developed by Nicolaides et al. [16]. According to standard definition, low birth weight and high birth weight were defined as a birth weight of less than 2500 g and more than 4000 g, respectively. SGA was defined as a weight below the 10th percentile for gestational age, while large for gestational age (LGA) indicated fetuses with a weight above the 90th percentile for the gestational age, calculated using a standardized reference chart [16].

Differences in rates of preterm deliveries, percentages of SGA and LGA across the two methods of pregnancy dating were analyzed.

Sample size and statistical analysis

Data was reported as mean \pm SD, median [interquartile range-IQR] or number (percentage) and compared using Student *t* test, non-parametric Mann-Whitney test, or Fisher exact test, or Wilcoxon test, as appropriate. Shapiro-Wilk test was preliminary performed to assess the consistency of the data with normal distribution. P values below 0.05 were considered statistically significant. All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS, version 23, Chicago, IL, USA). The 95%CI of proportions was calculated using a binomial distribution model. To calculate the sample size, we stated as clinically relevant a difference between GA_{IVF} and GA_{US} of 4 or more days in at least 15% of cases with a 95%CI of \pm 5%. On these bases, we needed at least 200 cases. This 15% rate was chosen among the authors based on discussion without a priori analyses on the impact of this delay on obstetrics care.

Results

Overall, 249 singleton pregnancies conceived by IVF were selected: 111 pregnancies (45%) were achieved by conventional IVF, while 138 (55%) were achieved by ICSI. Among the included women, 127 (51%) pregnancies resulted from frozen-thawed embryo transfer.

Baseline characteristics of the studied cohort are shown in Table 1. Women had a median age at the onset of pregnancy of 36 [34 – 39] years and most of them (203, 82%) were primiparous (Table 1).

At first trimester ultrasound scan, the discrepancy in days between GA_{US} and GA_{IVF} was \geq 4 days in 32 cases (13%, 95%CI: 9–18%). It ranged within 2 and 3 days in 100 cases (40%, 95%CI: 34–47%). In 117 cases (47%, 95%CI: 41–53%) GA_{US} and GA_{IVF} overlapped or showed a discrepancy of \pm 1 day.

Table 1. Baseline characteristics of the studied women (n = 249).

Characteristics	Median [IQR] or Number (%)
Age (years)	36 [34 – 39]
BMI (Kg/m ²)	22.0 [20.2–24.3]
Ethnicity	
Caucasian	245 (98%)
East Asian	3 (1%)
South Asian	1 (1%)
Smoking	9 (4%)
Previous deliveries	46 (18%)
Pre-gestational diabetes	0 (0%)
Chronic hypertension	2 (1%)
Cause of infertility	
Male factor	77 (31%)
Female factor	74 (30%)
Mixed	41 (16%)
Unexplained	26 (10%)
Not Available	31 (13%)
Type of transfer	
Fresh embryo transfer	122 (49%)
Frozen embryo transfer	127 (51%)

IQR: Interquartile Range. BMI: Body Mass Index.

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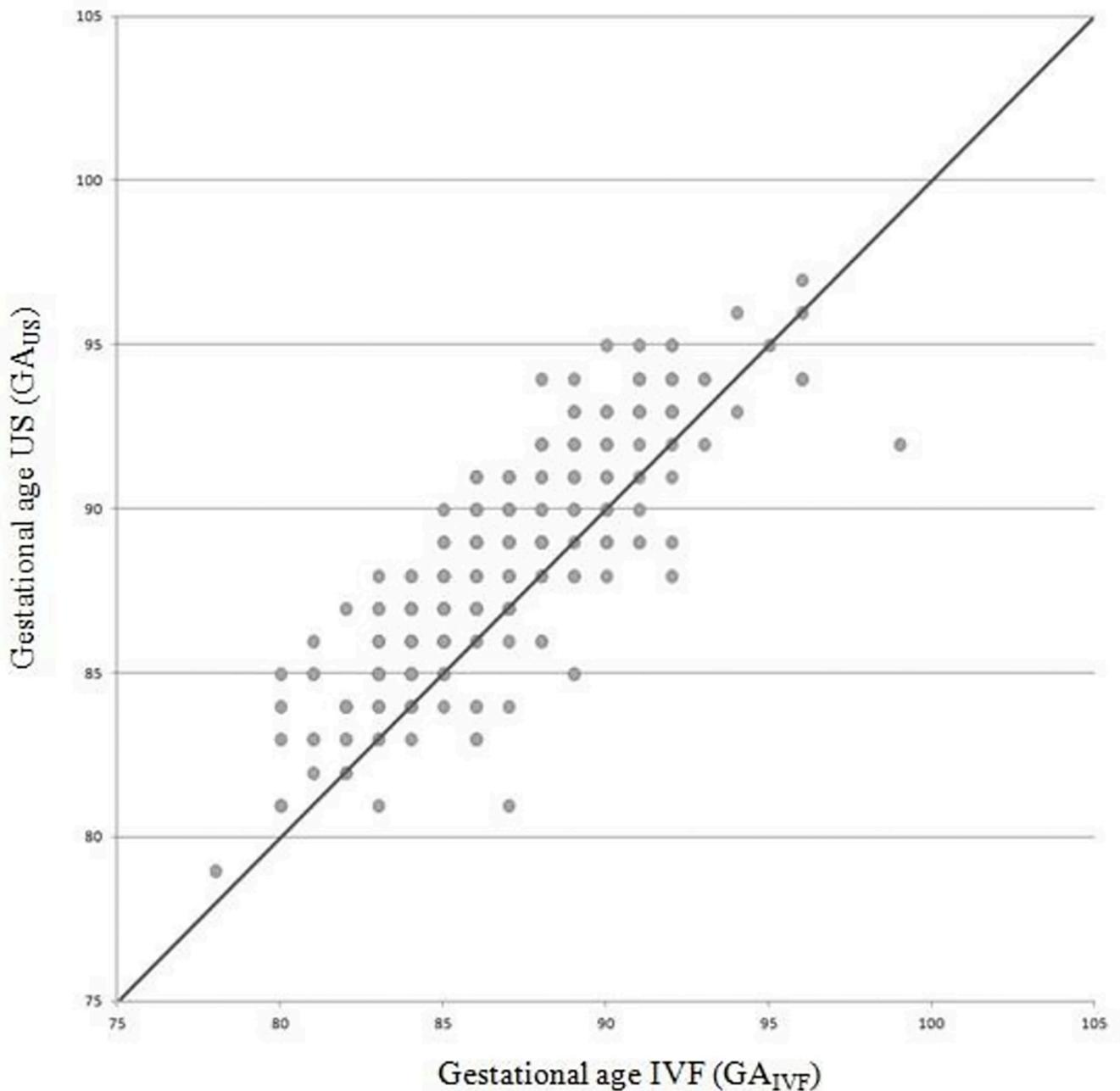


Fig 1. Comparison of GA obtained at the time of first trimester scan according to the two alternative pregnancy dating methods, on the basis of the IVF procedure (x axis), or on the basis of ultrasound measurement of CRL (y axis). The continuous oblique line represents the bisect (one should expect cases to be along the line if the two methods coincide). Most cases are located above the line. Intergroup comparison using paired non-parametric Wilcoxon test highlights a statistically significant difference ($p < 0.001$).

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Fig 1 shows the comparison between GA_{US} and GA_{IVF} at first trimester ultrasound scan. The median values of GA were 88 [86–91] days and 87 [85–90] days, respectively ($p < 0.001$). The median difference was 1 [0 – 2] days, with GA_{US} systematically higher than GA_{IVF} with most data points falling above the line that identified GA estimation according to ART procedures (Fig 1).

Table 2. Differences between GA_{US} and GA_{IVF} according to IVF modalities.

	Number	GA _{US}	GA _{IVF}	GA _{US} —GA _{IVF}	P
Fertilization method					
Conventional IVF	111	89 [86–91]	87 [85–90]	1 [0–2]	< 0.001
ICSI	138	88 [85–91]	87 [85–89]	1 [0–2]	< 0.001
Stage of embryo transfer					
Cleavage stage	144	88 [86–91]	87 [85–90]	1 [0–2]	< 0.001
Blastocyst stage	105	88 [86–91]	87 [85–89]	1 [0–3]	< 0.001
Fresh or frozen transfer					
Fresh	122	88 [86–91]	87 [85–90]	1 [0–2]	< 0.001
Frozen	127	88 [86–91]	87 [85–90]	1 [0–2]	< 0.001

Data is presented as median (Interquartile Range–IQR).

GA_{US}: Gestational age based on ultrasound. GA_{IVF}: Gestational age based on IVF procedures.

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Table 2 shows the discrepancy between GA_{US} and GA_{IVF} at first trimester ultrasound scan according to IVF procedures (conventional IVF or ICSI, transfer of fresh or frozen embryos, transfer at cleavage or blastocyst stage). A significant difference of about 1 day emerged in all subgroups tested.

Obstetric outcomes are shown in Table 3. The impact of the dating method on the duration of pregnancy and on the rate of abnormal fetal growth is illustrated in Table 4. Duration of pregnancy differ but no significant difference emerged for the rate of preterm birth or abnormal growth.

Discussion

Our study confirms a discrepancy between clinical and ultrasound dating of IVF pregnancies. More specifically, ultrasound measurements appeared to be greater compared to clinical

Table 3. Obstetric outcomes of the studied cohort (n = 249).

Characteristics	Median [IQR] or Number (%).
Pregnancy complications	
Gestational Diabetes	8 (3%)
Gestational hypertension	15 (6%)
Preeclampsia	2 (1%)
Placenta praevia	10 (4%)
Abruptio placenta	1 (1%)
Cholestasis	11 (4%)
Oligoamnios	16 (6%)
Polydramnios	5 (2%)
Mode of delivery	
Spontaneous vaginal delivery	108 (43%)
Operative vaginal delivery	24 (10%)
Elective caesarean delivery	65 (26%)
Urgent caesarean delivery	52 (21%)
Newborn	
Birthweight (g)	3,180 [2,843 – 3,503]
Low birthweight (<2,500 g)	18 (7%)
High birthweight (>4,000 g)	7 (3%)

IQR: Interquartile Range.

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Table 4. Duration of pregnancy and fetal growth according to the dating method.

Characteristics	GA _{US}	GA _{IVF}	P
Duration of pregnancy			
Length of pregnancy in days	274 [269–281]	273 [268–280]	<0.001
Preterm deliveries (<259 days)	20 (8%)	22 (9%)	0.87
Abnormal fetal growth			
Birth weight <10 percentile	49 (20%)	47 (19%)	0.91
Birth weight <5 percentile	26 (10%)	23 (9%)	0.76
Birth weight >90 percentile	14 (6%)	17 (7%)	0.71
Birth weight >95 percentile	9 (4%)	11 (4%)	0.82

Data is reported as median (Interquartile Range–IQR) or Number (%).

GA_{US}: Gestational age based on ultrasound. GA_{IVF}: Gestational age based on IVF procedures.

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dating. The magnitude of the phenomenon was overall modest, the median difference being +1 [IQR: 0–2] day, but in about one in eight women the discrepancy was more than 4 days (13%, 95%CI: 9–18%). This difference persisted regardless of the IVF modality performed, suggesting that this difference is exclusively attributable to the procedure *per se* rather than to some specific conditions of embryo culture. In other words, it is possible that the beginning of embryonic development is slightly anticipated in IVF pregnancies compared to natural conceptions, but neither the insemination technique, nor cryopreservation, nor the extended embryo culture seem to play a role in determining this phenomenon. Finally, the study showed that the existing discordance between GA_{US} and GA_{IVF} did not have a significant clinical impact with a similar rate of preterm birth and SGA between the two dating methods.

An accurate and reliable assessment of GA and estimated date of delivery (EDD) is a key component for a good obstetric management. At first glance it might seem that the calculation of GA is very straightforward, but we have different methods of gestational age assessment, each with their own strengths and weaknesses, that deserve careful consideration [17–19]. Evidence deriving from spontaneous pregnancies showed that the method of dating chosen, even in cases where there is a minimal discrepancy, can potentially influence obstetric management and obstetric practices, such as the use of antenatal corticosteroid therapy, labor induction in prolonged pregnancy, or estimation of fetal biometry and growth with its potential sequelae [20–24].

In clinical practice, standard calculation of GA for spontaneously conceived pregnancies relies on the difference between the EDD and date of last menstrual period (LMP). The EDD calculated from LMP is based on the assumption that the pregnancy lasts 280 days from the first day of the LMP [25]. It is widely recognized that this approach is laden with potential error because it is based on the accurate recall of the first day of the LMP. Indeed, if the LMP date is forgotten, if women have irregular menses or even if they don't want to report this information to their obstetrician, LMP could be calculated imprecisely [26]. Moreover, this method does not take into account the highly variable duration of the follicular phase of the menstrual cycle, which can range from 7 to 21 days [27,28]. Calculation of GA from LMP has now been substituted or implemented by predictions based on early ultrasound dating through CRL measurement [20,21]. The issue regarding which of these methods guarantees a more accurate estimation of GA has been the center of debate for a long time. However, as far as spontaneous pregnancies are concerned, it is widely accepted that, when performed with quality and precision, the measurement of CRL is the most reliable method to establish GA, offering the advantage of greater objectivity and reproducibility and overcoming the limits of the

anamnesic assessment [22–24]. In pregnancies conceived through IVF, we know the exact date of the conception from the day of oocyte retrieval, but we can count on ultrasound biometry as well [25,26].

Currently, the vast majority of guidelines agree in considering GA_{IVF} as the optimal method to establish the EDD in IVF pregnancies [13,29,30]. However, studies on first-trimester fetal growth trajectories in IVF pregnancies have not led to consistent findings, possibly due to differences in study design or study population or insufficient statistical power. Eindhoven et al. found similar first-trimester growth trails between pregnancies conceived by IVF ($n = 58$) and spontaneously conceived ($n = 88$) pregnancies in healthy women [31]. Conway et al. also did not identify significant differences in CRL measurement at 9–12 weeks' gestation among women who conceived by IVF ($n = 63$), ART other than IVF ($n = 64$), or spontaneous conceptions ($n = 1535$) [32]. On the other hand, the studies that included a larger number of cases highlighted a difference. Bonne et al. reported that first-trimester CRL measurements obtained in pregnancies conceived through IVF ($n = 529$), including both fresh and frozen embryo-transfer, were increased by an average of 1.5 days compared to spontaneous pregnancies ($n = 6,621$) at the same gestational ages [33]. These findings are in accordance with the results of a study published by a British group in 2018, which included 178 IVF pregnancies and showed that the CRL reference charts currently used in clinical practice would appear to overestimate GA, the difference being on average three days longer when applied to IVF pregnancies [34]. Our results are in line with these two latter studies, even if the detected magnitude of the difference was milder (median of 1 day).

Our study could not provide evidence to explain the gap between GA_{US} and GA_{IVF} . However, some points deserve to be emphasized. It has firstly to be noted that there is still a lack of precise information regarding the time span between ovulation and fertilization, and between fertilization and implantation in natural conditions. One could hypothesize some discrepancies between IVF and natural pregnancies during the course of these steps [35]. This may be particularly likely for the first part, i.e. the time lapse between ovulation and fertilization. In fact, oocytes are commonly retrieved several hours before the natural ovulation and they are fertilized soon after the retrieval (typically three-four hours later) [36–38]. In addition, in frozen cycles, thawed embryos are typically kept in culture for some hours, if not overnight. This may also anticipate the embryo development compared to natural conditions. This may not occur so rapidly in natural conditions and may explain at least in part the one-day delay emerging from our findings.

An alternative explanation for the gap between GA_{US} and GA_{IVF} dating could be related to the culture of the embryo in *in vitro* conditions and its transfer within a highly perturbed uterine cavity [39]. The culture media were indeed shown to influence fetal growth [40] and the supra-physiological hormonal condition of a fresh cycle can anticipate the window of implantation, with possible impact in the first stages of embryo development [39]. However, our observations that the gap was present regardless of the insemination technique (classical IVF versus ICSI) or the embryonic stage at the time of transfer (cleavage stage or blastocyst stage) argue against an effect *in vitro*. Moreover, the observation that a delay of one day persisted even when restricting the analysis to frozen cycles does not support a detrimental effect of the disrupted hormonal milieu.

IVF pregnancies are recognized to have a higher risk of adverse perinatal outcome. Previous studies on IVF pregnancies demonstrated that they are complicated by higher rates of preterm infants [41], intrauterine growth restriction and SGA and a higher risk of low birthweight [41] compared to spontaneously conceived pregnancies [42,43]. In the present study no differences were shown in the rate of pre-term deliveries and SGA newborns, comparing the use of GA_{US} to GA_{IVF} . This could be expected given the modest magnitude of the detected difference.

Compared to naturally conceived pregnancies, our study showed that ART pregnancies account for a higher-than-expected number of SGA infants regardless the methods of pregnancy dating used (18% according to GA_{US} and 16% according to GA_{IVF} rather than the expected 10%), similarly to what previously observed by Wennerholm et al. and Tan et al. [42,43]. Conversely, the overall percentage of LBW infant was essentially coherent.

Some limitations of the study need to be considered: this is a retrospective study and thus exposed to the inaccuracies of this study design. Moreover, being a single-centre study, the sample size is relatively small. In order to confirm the existence of this discrepancy in the calculation of gestational age, further studies, would be necessary, preferably multicenter ones, to reach a greater numerosity.

Conclusions

The median delay between GA_{US} and GA_{IVF} is generally modest. Nevertheless, in one in eight women the difference overcomes four days. Such a proportion cannot be overlooked, since it may cover clinical relevance, especially in those centers with a high turnout. To date, there is no evidence to draw firm conclusions on the most appropriate method of dating for IVF pregnancies. Despite a known date of conception, it is however difficult to assume that the oocyte retrieval date precisely resembles the date of natural ovulation and conception. The steps of oocytes retrieval and fertilization are significantly anticipated in IVF pregnancies. In contrast, there is insufficient evidence to hypothesize an accelerated growth consequent to *in vitro* culture media conditions or *in vivo* environmental influences. In other words, IVF would anticipate fertilization, it would not accelerate embryo development. From this point of view, ultrasound evaluation of GA is more reliable and replicable. Although it is based on operators' skill, it is not as operator dependent as it seems: if the Fetal Medicine Foundation criteria are met, differences in the measurement of the CRL are only a few millimeters and do not affect the final determination of the correct gestational age. On these bases, we suggest to date IVF pregnancies using GA_{US} because it could realign IVF pregnancies to natural pregnancies.

Supporting information

S1 Database.

(XLSX)

Author Contributions

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