Influence of medically assisted reproduction techniques on crown-rump length and biochemical markers of trisomy 21 in the first trimester of pregnancy

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Objective: To determine whether there is a difference between the known gestational age in pregnancies conceived after IVF and the estimated gestational age based on the crump-rump length (CRL) measurement during the first trimester.
Design: We retrospectively (between 2007 and 2012) studied a cohort of 6,739 patients who underwent ultrasonography between 11 and 13+6 weeks of amenorrhea.
Setting: All of the ultrasonograms were performed at the Centre Médico-Chirurgical et Obstétrique, Strasbourg, France.
Patient(s): Group A consisted of 6,621 patients with regular menses whose term was calculated based on the date of their last menstrual period (LMP). Group B consisted of 529 patients whose pregnancies had been achieved by IVF and in whom term was calculated based on the date of fresh or frozen ET.
Intervention(s): None.
Main Outcome Measure(s): The gestational age difference was obtained by measuring the CRL (Robinson's curve) and the gestational age calculated in accordance with the LMP or the ET day was measured in each group.
Result(s): The gestational age difference was significantly more in group B (2.3 days vs. 0.84 days in group A). We found a significant difference regarding biochemical markers for trisomy 21 to the detriment of group B with a significantly reduced pregnancy-associated protein P-A multiple of median (0.78 vs. 0.92).
Conclusion(s): There appears to be a small difference in CRL development between spontaneous pregnancies and pregnancies conceived by assisted reproductive technology (ART). Specific ultrasonographic curves for pregnancies conceived by ART would be more relevant and precise. The underlying pathophysiological mechanisms are not very clear and offer possibilities for future research. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: ART, CRL, early fetal growth, PAPP-A, hCG

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In France 21,000 infants are born each year after the use of an assisted reproductive technique (ART) (1). Patients are not obliged to inform the obstetrician about the mode of conception, although this may be important for subsequent follow-up of the pregnancy and when screening for trisomy 21. In addition, very few studies have examined the effect of ART on crown-rump length (CRL). In a population of 729 singleton pregnancies conceived by ART Gjerris et al. (2) found a significant difference of 1.5 days longer between the gestational age measured on the basis of the CRL and the gestational age calculated according to the date of ET. Tunon (3) and Sladkecivius (4) and their colleagues found that CRL was shorter than expected based on Wisser's curve (which was established in a population of pregnancies conceived by IVF). None

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of these studies, however, had a control group, which might have validated the outcome.

We therefore decided to study the CRL. The initial issue in the first trimester was determining dates for the pregnancy.

Fetal growth in the first trimester of pregnancy is homogeneous from one pregnancy to the next, which enables the age of the pregnancy to be determined based on the CRL. Equations have been devised (e.g., Robinson's curve, Wisser's curve) that make it possible to specify the gestational age according to the CRL. The CRL is used in everyday practice to date pregnancies.

The other issue in the first trimester of pregnancy is screening for trisomy 21 by integrating its serum marker assay results with nuchal translucency measurements. The literature suggests a trend for pregnancy-associated protein P-A (PAPP-A) multiple of median (MoM) levels to be lower and for hCG MoM to be higher. Results are summarized in Table 1 (7–27). We therefore wished to study our own population to determine the influence of ART on CRL and to verify the influence of ART on nuchal translucency measurement and first trimester serum markers when screening for trisomy 21.

The principal objective of the study was to determine whether there is a difference between the known gestational age in pregnancies conceived after IVF and the estimated gestational age based on CRL measurement during the first trimester. The secondary objective was to test for a difference in the PAPP-A MoM, hCG MoM, and nuchal translucency measurement MoM in patients whose pregnancy was conceived by IVF versus the expected parameters in patients who became pregnant spontaneously.

MATERIALS AND METHODS

This was a retrospective cohort study that enrolled 6,739 patients who underwent obstetrical ultrasonography during the first trimester (between 11 and 13+6 weeks of gestational age) of their pregnancy at the antenatal unit of the Strasbourg Medico-Surgical and Obstetrical Center between January 1, 2007 and July 21, 2012. Only patients with the following characteristics were included: [1] with a singleton pregnancy; [2] of those pregnancies conceived by ART, only those obtained after IVF, intracytoplasmic sperm injection (ICSI), or frozen ET; [3] only patients reporting regular 28-day menses

TABLE 1

Results of the principal studies on the influence of ART on early markers for trisomy 21.

Author		Type of pregnancy	Number of patients	MoM PAPPA	*P* value	MoM hCG	*P* value
Anckaert et al. (2008)		Spontaneous	4.088	1.1		0.97	
		IVF	59	0.75	.002	0.9	.002
		ICSI	163	0.94	.002	1.07	.002
		TEC	31	1.05	.002	1.12	.002
		Male infertility	108	0.92	<.04	0.87	<.04
		Female infertility	96	1.14	<.005	0.93	<.005
Amor et al. (2009)		Spontaneous	50.253	1.02		0.99	
		IVF	513	0.87	<.001	1.01	.601
		ICSI	833	0.84	<.001	1	.563
		TEC	573	0.95	.001	1.03	.06
Bellver et al. (2005)		Spontaneous	498				
		IVF	47	1.06	<.05	0.83	.002
		ICSI	222			1.13	.002
Bender et al. (2010)		Spontaneous	1.341	1.06		0.94	
		IVF	110	0.86	<.001	1.1	<.005
		ICSI	331	0.9	<.001	1.1	<.005
Bersinger et al. (2004)	10–12 SA	Spontaneous	57	3.11 (mIU/mL)		6.12 (mIU/mL)	
		IVF	9	1/89 (mIU/mL)	NS	7.88 (mIU/mL)	NS
		ICSI	18	1.66 (mIU/mL)	<.01	6.78 (mIU/mL)	NS
	12–14 SA	Spontaneous	48	61,910 (mIU/mL)	NS	55,721 (mIU/mL)	NS
		IVF	14	81,597 (mIU/ml)	NS	70,069 (mIU/mL)	NS
		ICSI	18	76,964 (mIU/mL)	NS	79,591 (mIU/mL)	NS
Ghisoni et al. (2003)		Spontaneous	429	1.02		0.99	
		AMP	145	0.98	.5	1.12	.002
Gjerris et al. (2009)		Spontaneous	2,532	0.98		0.99	NS
		IVF	512	0.78	<.001	0.96	NS
		ICSI	396	0.79	<.001	0.98	NS
		TEC	84	1.03	<.001	1	NS
Liaoi et al. (2001)		Spontaneous	1,233	1.09		1.06	
		IVF	220	1	.58	1.21	1.09
		ICSI	30	0.86	.39	1.09	.62
Orlandi et al. (2002)		Spontaneous	370	1		1	
		IVF	32	0.79	.0023	1.1	.3717
		ICSI	42	0.96	.4178	1.02	.8193

Note: AMP =; ART = assisted reproductive technology; MoM hCG = multiple of median human chorionic gonadotropin; MoM PAPPA = multiple of median pregnancy-associated protein P-A; NS = not significant; SA =; TEC = .

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