Premature Birth, Low Birth Weight and Birth Defects after Assisted Reproductive Therapies. A 18-Year Comparative Study

Risques de Prématurité, de faible poids de naissance et de malformations congénitales après assistance médicale à la procréation: étude comparative sur 18 ans.

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R É S U M É

Introduction : Les techniques de la procréation médicalement assistée (PMA) sont devenues de pratique courante en Tunisie. Il était pertinent de définir les risques périnataux associés à ces nouvelles thérapies. Le risque de naissances multiples et leurs corollaires après PMA sont bien admis. Nous avons étudié les risques périnataux chez les singletons et les jumeaux de PMA par rapport à la conception naturelle.

Méthodes : C'est une étude rétrospective, descriptive et comparative, incluant tous les nouveau-nés conçus par PMA et admis entre 1998 et 2015 et des nouveau-nés spontanés choisis au hasard durant la même période.

Nous avons comparé séparément les singletons et les jumeaux entre PMA et conception naturelle pour les risques de prématurité et de faible poids de naissance (FPN). Pour les malformations congénitales (MC), nous avons comparé les deux groupes regroupés.

Résultats : Nous avons identifié 425 nouveau-nés de PMA et 322 issus d'une grossesse spontanée. Le risque de prématurité était significativement plus élevé chez les singletons et les jumeaux de PMA par rapport aux spontanés. Chez les singletons, la PMA était associée à des taux significativement accrus de FPN et de très faible poids de naissance (TFPN). Pour les jumeaux, ce résultat était valable seulement pour le TFPN. Les nouveau-nés de PMA avaient un risque de MC trois fois supérieur à celui des spontanés. Les risques de MC étaient significativement plus élevés avec l'injection intra cytoplasmique de spermatozoïdes (ICSI), les inducteurs de l'ovulation et la fécondation in vitro. Les risques de MC étaient 2,4 fois plus élevés avec l'ICSI qu'avec toutes les autres thérapies regroupées.

Conclusions : Cette étude a mis en évidence les risques périnataux accrus de la PMA comparativement à la conception naturelle même chez les singletons. Les mécanismes sous-jacents exacts de tous ces risques restent flous. D'autres études sont nécessaires pour prouver la part de la PMA, des caractéristiques parentales et des facteurs liés à la stérilité elle-même.

M o t s - c l é s

Procréation médicalement assistée, injection intra cytoplasmique de spermaozoides, Fécondation In Vitro, inducteurs de l'ovulation, insémination avec sperme du conjoint, prématurité, faible poids de naissance, malformations congénitales

S U M M A R Y

Background: As assisted reproductive therapies (ART) become more common in Tunisia, it was relevant to define the associated perinatal risks. The risk of multiple births and its correlate after ART were well admitted. We aimed to disclose whether ART were associated with increased perinatal risks in singletons and twins from ART comparatively with spontaneous conception.

Methods: A retrospective descriptive and comparative study including all newborns conceived by ART and admitted between 1998 and 2015 and spontaneous newborns selected randomly.

We compared separately singletons and twins from ART and natural conception for premature birth (PB) and low birth weight (LBW). For birth defects (BD), we compared the two groups condensed.

Results: We identified 425 ART newborns and 322 controls. The risk of PB was statistically higher, in both ART singletons and twins than in controls. Among singletons, the use of ART was associated with statistically significant increased rates of LBW and VLBW. Among twins, this result was valuable only for VLBW. Newborns conceived with ART had a risk of BD that was three times higher than in controls. BD risk was statistically higher with ICSI (Intra Cytoplasm Sperm Injection), ovulation inductor and in vitro fertilization. BD risks were 2.4 times higher with ICSI than with all others therapies condensed.

Conclusions: This study highlighted the increased perinatal risks even in singleton from ART comparatively with natural conception. The exact mechanisms underlying all these risks remain unclear. Further studies are required to prove the part of ART underlying parental factors, and sterility itself.

K e y - w o r d s

Assisted reproductive technologies; In vitro fertilization; Intra Cytoplasm Sperm injection; Ovulation Induction; Intra Uterine Insemination; Premature; Infant; Low birth weight; Infant; Very low birth weight; Birth defects; Congenital abnormalities.

Assisted reproductive therapies (ART) offer hope to subfertile couples and has progressed from experimental treatment to routine practice in the majority of countries. An estimated 5 million ART children were born worldwide to date (1). In occident, ART newborns represent 1 to 3 % of the general birth population (2). Tunisia, where the practice of ART began in 1986, was the pioneer in Maghreb countries in this domain. Since the first Tunisian birth after Intra cytoplasm Sperm Injection (ICSI) in1996 (3), ART became more common. Thus, it was relevant to define and understand the associated perinatal risks in the interest of current and future ART children, and to undertake informative counseling of couples seeking ART. Current evidence suggests that ART does increase risks of higher order pregnancy with its inherent pre-and perinatal risks; especially premature birth (PB) and low birth weight (LBW). For birth defects (BD), literature data are variable depending on the type of ART. The two main objectives of this study were to determine if ART singletons and twins have increased perinatal risks comparatively with those naturally conceived, and if ARTs are associated with a higher risk of BD.

METHODS

Study design/setting:
A retrospective, descriptive and comparative single-center study including two groups of newborns admitted in the Neonatal intensive Care unit of the Military Hospital of Tunis was conducted between 1998 and 2015.

Patients: The first group included all newborns conceived by ART (ART group). Both inborn and out born neonates from ART were included. In vitro fertilization (IVF), ICSI, Ovulation Induction (OI) and Intra Uterine Insemination (IUI) were considered as ART in the present study. The second group included naturally conceived singletons and twins admitted during the same period and selected randomly (Controls group). Data collection was done from the medical birth records, the admissions register and the medical records after hospitalization. Further information was obtained from outpatient medical records.

Outcomes Measures/ comparison:
We first accomplish a descriptive study regarding the characteristics of the ART group. Then, we compared separately, singletons and twins between ART and natural conception for the following outcomes: PB, very PB (VPB), LBW, very low birth weight (VLBW). For BD, we compared all newborns of the two groups condensed.
We considered PB before 37 gestational weeks (GW); VPB before 32 GW; LBW less than 2500 g and VLBW less than 1500 g.

Definition of Major/minor birth defects: Congenital malformation or BD was defined as a physical anatomical anomaly detected at birth and listed in the International statistical classification of diseases and related health problems (4). Classification of major or minor BD was based on its risk to the child's life and cosmetic significance (5). Anomalies were certified and classified after an assistant or a professor medical doctor examination. A case was classified into an organ system including chromosomal abnormality and counted only once in each organ system. A case with multiple major anomalies was counted in several groups according to the organ systems affected.

Statistical analysis:
Data analysis was performed using the Epi info software package version 7.1.5. Means and odds ratio (OR) were given with a confidence interval (CI) of 95%. The differences in outcomes were analyzed using Chi 2 test for percentages. Fisher's exact probability test was used in cases where the expected frequency was less than five. Statistical significance was determined at a p value of < 0.05. OR is the number of times by which the probability of a neonatal outcome is multiplied in exposed newborns (ART group) in comparison with non-exposed newborns (Controls group).

RESULTS

1-General Data: During the study period, we admitted 425 neonates from ART (122 singletons, 181 twins and 122 newborns issued from a multiple pregnancy ≥ 3 fetuses) representing 2.7% of total admissions. This population included 12 stillbirths. The control group included 322 newborns (141 singletons and 181 twins naturally conceived).

2- Characteristics of Births after assisted reproductive therapies:
Table 1 presents the general characteristics of the ART group newborns.
Women who received ART were older than 30 years in 55% (versus 42.5% in the control group; $p = 0.005$).Their age ranged between 19 and 42 years with a mean of 32.9 ± 4 years (versus 30.7 ± 5 years in the control group, $p < 0.001$). The sex ratio (Male/female) of the ART group newborns was 1.08.
Among ART group, the rate of multiple births (≥ 2 fetuses) was 71.3%. The rate of high ranking multiple births (≥ 3 fetuses) was 28.7% (table1).

2-Comparative study of singletons and twins: ART versus natural conception
2-1-Premature Birth:
The distribution of the study population according to the rate of PB was presented in table 2. The risks of PB and VPB were significantly higher, both in singletons and in twins from ART than in controls (Table 2).

Table 1 : General characteristics of ART group

Parameters		ART (N=425) N(%)
Maternal age (y)	mean ±SD	32.9 ±4
	>35	85 (20)
Parity	Nulliparity	359 (84.5)
ART	IVF	140 (33)
	OI	131(30.8)
	ICSI	114 (26.8)
	IUI	40 (9.4)
Fetus number	1	122 (28.7)
	2	181(42.6)
	3	114 (26.8)
	4	8 (1.9)
	Vaginal delivery	123 (29)
Delivery mode	Caesarean section	302 (71)
	Male	221 (52)
Sex	Female	204 (48)
	<37GW	292(68.7)
Term	<32 GW	97 (22.8)
	Mean	2940±560
Birth Weight (g)	LBW	297(69.8)
	VLBW	73 (17.17)

ART: assisted reproductive therapies; g: gram, GW: gestational weeks, ICSI: Intra Cytoplasmic Sperm Injection; IUI: intrauterine insemination; IVF: In vitro fertilization; OI: ovulation induction; LBW: Low Birth weight; SD: standard deviation; VLBW: Very Low Birth weight, y: year.

Table 2: Premature birth rates for the ART and control groups

	Singletons			Twins		
Birth Term	**ART N (%)**	**Controls N (%)**	**P OR (CI)**	**ART N(%)**	**Controls N(%)**	**P OR(CI)**
<37GW	37 (30.3)	24 (17)	0.01	135 (74.6)	103 (57)	0.0003
<32GW	14 (11.4)	3 (2.1)	2.1 (1.2-3.9)	54 (29.8)	9 (4.9)	2.2 (1.4-3.4)
			0,004			<10 -3
			6 (1.6-21)			8.1 (3.7-19)
TOTAL	122	141	-	181	181	-

ART: assisted reproductive therapies, CI: confidence interval; g: gram; N: number, OR: odds ratio

2-2-Low birth weight:

Table 3 summarized the distribution of the population according to the rates of LBW and VLBW. Among singletons, the use of ART was associated with significantly higher rates of LBW and VLBW than in controls. Among twins, this result was valuable for VLBW but not for LBW.

2-3 Birth defects:

The BD related data were listed in Table 4. The overall risk of BD was three times higher in ART group than in controls. The major BD rate was 3.4 times higher in the ART group. The difference was not statistically significant for minor BD. The difference between the two groups was significant in the ART group as shown in the table 5.

Table 3: Low birth weight rates for the ART and control groups

	Singletons			Twins		
	ART N (%)	**Controls N (%)**	**P OR (CI)**	**ART N(%)**	**Controls N(%)**	**P OR(CI)**
<2500 g	72	26	$<10^{-3}$	120	120	0,99
	(51)	(18.7)	6.3 (3.6-11)	(66.3)	(66.3)	$<10^{-3}$
<1500 g	26	3	$<10^{-3}$	60	9	9.4
	(18,7)	(2.1)	12,4	(33.1)	(4.9)	(4-19.8)
			(3.6-42.3)			
TOTAL	122	141	-	181	181	-

Table 4 : Birth defects rates for the ART and controls groups

	N	All BD N (%)	P OR (CI)	Majors BD N (%)	P OR (CI)	Minors BD N (%)	P OR (CI)
ART	425	47 (11.05)	10^{-4}	34 (8)	0.001		0.1
						13 (3.05)	
Controls	322	12 (3.7)	3.2	8	3.4		2.5
			(1.6- 6.7)	(2.4)	(1.5-8.6)	4 (12.1)	(0.7-10.6)

Table 5: Birth defects by affected organ system for the ART and control groups

Birth defect (isolated or associated)	ART N= 425		Controls N=322		P	OR (CI)
	N	%	N	%		
Cardiac	19	4.5	2	0.6	0.003	7,5 (1,7-66,6)
Musculo-skeletel	16	3.7	7	2.17	0.3	1.7(0.7-4.33)
Neurologic	13	3.05	0	0	<10-3	undefined
Urogenital	6	1.4	3	0.9	0.7	1.5 (0.4-6)
Digestive system	5	1.18	2	0.6	0.7	1.9 (0.36-9.9)
Respiratory	4	0.9	2	0.6	0.7	1.5 (0.2-8.3)
Chromosomic	4	0.9	3	0.9	1	1 (0.2-4.5)
Ocular	1	0.23	0	0	1	undefined
Diaphragmatic hernia	3	0.7	0	0	0.26	undefined
Multiple	15	3.5	5	1.55	0.1	2.3(0.7-8.2)

ART: assisted reproductive therapies, CI: confidence interval; N: number, OR: odds ratio

In the ART group, BD (N=47) were associated with ICSI in 44.7% (21 of 47) of cases, OI and IVF in 25.5% of cases each one (12/47) and IUI in 4.25% (2/47) of cases. The BD rates according to the therapy used and their comparison with controls were listed in the table 6. This table showed that the difference between the ART and the control groups was statistically significant only for ICSI, IVF and OI. Otherwise, the comparison of the different therapies with each other founded that the BD rate was 2.4 times higher with ICSI (18.4%) than with all other therapies condensed (8.03%), (p=0.006; OR:2.4, 95% CI; 1.3 to 4.5). ICSI was also 2.4 times more associated with

BD than IVF (p=0.03, OR: 2.4; 95%CI: 1.1-5.1). The difference was not significant between FIV/ICSI (33/255) and OI/IUI (14/170) condensed (p=0.2; OR: 1.6; 95%CI: 0.8-3.2).
For major BD, the difference with controls was confirmed only for ICSI and OI as shown in table7. ICSI was 3 times more likely associated with major BD than IVF (p=0.02; OR: 3; 95%CI: 1.2-7.8).
Among the 47 malformed ART newborns, 16 were dead. BD were the cause of death in 23.4% (11 of 47), and associated with a major handicap in 22.6% (7/13) of the survivors.

Table 6: Birth defects and type of ART

ART	N	Birth defects N (%)	P	OR (95 % CI)
ICSI	114	21(18.4%)	<0.01	5.8 (2.7-12.3)
OI	130	12 (9.2%)	0.03	2.6 (1.1-6)
IVF	141	12 (8.5%)	0.05	2.4 (1.05-5.4)
IUI	40	2 (5%)	0.6	1.3 (0.3-6)
Controls	322	12 (3.7%)	-	-

ART: assisted reproductive therapies; CI: confidence interval; ICSI: Intra Cytoplasm Sperm Injection, IUI: intrauterine insemination; IVF: In vitro fertilization; N: number, OR: odds ratio; OI: ovulation induction

Table 7: Major birth defects and type of ART

ART	N	Major BD N (%)	P	OR
ICSI	114	16 (14.03)	$<10^{-3}$	10.3 (3.7-28.9)
OI	130	9 (6.92)	0.007	4.7 (1.5-14.3)
IVF	141	7 (4.96)	0.07	3.3 (0.8-13.4)
IUI	40	2 (5)	0.37	3.3 (0.3-21)
Controls	322	5 (1.5)	-	-

ART: assisted reproductive therapies; BD: birth defects; ICSI: Intra Cytoplasm Sperm Injection, IUI: intrauterine insemination; IVF: In vitro fertilization; N: number, OR: odds ratio; OI: ovulation induction

DISCUSSION

In spite of its retrospective and monocentric characters, the present study highlighted the increased perinatal risks even in singletons from ART comparatively with natural conception. ART is well recognized to be associated with twin and higher order pregnancies (6) as it was confirmed in the present study .Multiple pregnancies of whatever modes of conception are associated with an increased per, perinatal and childhood morbidity and mortality (7).
However, several individual and meta-analysis studies have suggested that, even, when considered separately, ART-conceived twins and singletons are subject to higher perinatal risks compared with those naturally conceived (8-12). It is not yet possible to study all forms of ART; only IVF, and ICSI have yielded sufficient data for formal systematic reviews (24-25).
In this study, we focused on PB, VPB, LBW, and VLBW being convinced that morbidity and mortality are essentially correlated.

Premature birth/ very premature birth:
ART newborns had a higher risk of PB (13-15). This issue was valuable even in singleton ART pregnancies. In fact, data from a meta-analysis by Jackson et al (10), which identified 15 studies comprising 12283 IVF and 1.9 million spontaneously conceived singletons, found that IVF singletons were associated with significantly higher odds of PB (OR 2.0; 95% CI 1.7–2.2), in comparison with singletons naturally conceived (10). More recently, Stojnic et al (11) had similar findings with a total PB rate of IVF pregnancies of 9.3%, versus 5.85% in controls (p<0.05), especially with VPB (11).
In our study, both ART singletons and twins were associated with a doubling in risks of PB and VPB.

Low birth weight/ very low birth weight:
Current data suggest that ART newborns have 2 to 3 times higher risk of LBW. This has been validated for both twins (8, 10, 16) and singletons (12, 14). In the meta-analysis by Jackson et al (10), IVF singleton pregnancies were associated with significantly higher odds of LBW (OR 1.8, 95% CI 1.4–2.2), and smaller for gestational age (OR 1.6, 95% CI 1.3–2.0); in comparison with singletons spontaneous conceptions (10). Ombelet et al (9) also found that, in ART singletons, LBW and VLBW were seen more often (<2500 g: **6** versus 3.7%, OR 1.86, CI 1.65–2.10; <1500 g: 1.3 versus 0.4%, OR 3.21, CI 2.31–4.47) (9).
Another study (11), interestingly, found that there were no differences in average birth weights, LBW, VLBW, small for gestational age regarding pregnancy origin.
In the present study, the risk of LBW was nearly four times higher only in ART singletons comparatively with controls. However, for VLBW, both ART singletons and twins were associated with higher risks than controls.
As supported by these data, multiple births may be partially responsible for PB and LBW in ART newborns; other factors are also responsible for these issues. In fact the link between the time to conceive (as an index of subfertility of the parents) and these factors has been established by Ghazi et al (17), thus linking them with subfertility rather than techniques used in ART (18).

Birth defects
Association between BD and ART was firstly raised in 1987 by Lancaster (19) who reported a higher number of BD in neural tube and transposition of great vessels in newborns from ART (19). Data from the following studies linked to ART were variable. Consistent evidence from individual studies, including registry-based cohort studies (20, 21) and meta-analyses, has linked ART involving IVF or ICSI with an increased risk of BD (22, 23). In the present study, this increase of BD rate was confirmed with

ICSI, IVF and interestingly with OI. The higher OR was noted with ICSI.

For major BD, several meta-analyses have concluded to a 30% increased risk in IVF or ICSI children's (prevalence up to 9.5 and 9.7% respectively) compared with natural conception (prevalence up to 6.9%)(7). Data of the present study founded no difference between IVF and controls for major BD. This difference was confirmed only for ICSI and for OI.

In a meta-analysis including 19 studies, Rimm et al (22) found that the rates of major BD ranged from 0 to 9.5% for IVF, 1.1 to 9.7% for ICSI, and 0 to 6.9% in the control groups. No significant difference between the ART therapies has been found in this meta-analysis (22, 24). These results had been corroborated by the large prospective study of Katalinic et al (25). In the present study, we reported a higher prevalence of major BD (14 %) than the rates reported in the literature (24). ICSI had the higher OR (10.3) and was 3 times more likely to be associated with major BD than IVF.

It is unclear whether the excess of BD after IVF or ICSI may be attributable to patient characteristics related to infertility (23), to the treatment, and whether risk is similar across ART and related therapies (22, 26, 27). This hypothesis was supported by the data provided by the present study showing an increased risk of BD with OI also and the absence of a statistically significant difference between FIV/ICSI and OI/IUI.

After adjustment of the preliminary results, the meta-analysis of Rimm et al (22) concluded that hypofertility was responsible of 40% of major BD in ART newborns.

Infertility has been suggested as a "*per se"* risk factor with retrospective studies detecting an increased frequency of chromosomal abnormalities in women and men undergoing infertility treatments (17, 24, 28). Even if the pathway(s) remain unclear, it has been suggested that the process of ART might influence epigenetic and, thus, imprinting changes in the developing embryo (7). This hypothesis was supported by a large scale studies/surveys concluding to an increased prevalence of Beckwith–Wiedemann syndrome and Angelman syndrome in ART children (18, 29-31). In addition, a third imprinting syndrome – maternal hypomethylation syndrome – has been linked to ART (32). Recent data concluded to a potentially link of ART with Silver-Russell syndrome (33). However, it is important to bear in mind that given the rarity of these disorders, absolute risks remain small (7).

CONCLUSIONS

This study highlighted the increased perinatal risks even, in singleton infants conceived with ART in comparison with those naturally conceived. Thus, multiple births may be only partially responsible of these risks in ART newborns. BD risk is also significantly increased in ART newborns. The exact mechanisms underlying all these risks remain unclear. Overall, couples with subfertility should be counseled regarding the increased risk of major BD. Although imprinting disorders, even with the increased risk identified, are rare in absolute numbers, couples with subfertility should be advised that these rare events seem to be more frequent than for fertile couples conceiving spontaneously (18). Further studies are required to prove the part of ART underlying parental factors, and sterility itself in ART risks. Follow up of the long-term health of ART children will remain important in the future. In Tunisia, it is time to think about creating a national register of ART where will be listed all ART cycles, pregnancies and birth outcomes.

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