No specific adverse pregnancy outcome in singleton pregnancies after assisted reproductive technology (ART) for unexplained infertility

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ABSTRACT.

Objective: To evaluate the obstetrical outcome of pregnancies obtained after assisted reproductive technology (ART).in women with unexplained infertility.

Materials and Methods: We conducted a retrospective observational case - control cohort study between January 2011 and May 2017. All pregnancies obtained after ART (Intra uterine insemination, In Vitro Fertilization, Intra Cytoplasmic Sperm Injection) were included. The ART pregnancy outcome of women with unexplained infertility was compared to ART pregnancies obtained in a context of male infertility. Cases were matched to controls (1:2) for age, Body Mass Index (BMI), and smoking status.

Results : After exclusion of twins, we studied 67 singleton pregnancies in the case group, matched with 129 singleton pregnancies in the control group. The first-trimester complications (miscarriage before 12 weeks gestation (WG), ectopic pregnancy) were similar in the two groups. Concerning the 2nd and the 3rd trimester, the incidence of gestational diabetes mellitus, pre-eclampsia, placenta previa, preterm labor was comparable between the two groups. In singletons, we found a non-significant increase of post-partum hemorrhage (OR=5.5, IC 0.5-50, p=0.13) and small for gestational age new-borns (OR=3.45, IC 0.65-18.1, p=0.14) in women with unexplained infertility.

Conclusion: More adverse obstetrical outcome are commonly reported after ART, even in singleton pregnancies. Little is known for explaining it and to distingue the own contributions of ART techniques and of the infertility etiology. In our study, we didn't observe a significant negative impact of a history of unexplained infertility on pregnancy. However, further large studies are needed to evaluate more accurately the possible responsibility of the infertility etiology on obstetrical and perinatal outcome.

Key words : Unexplained infertility, ART, pregnancy, outcome

Introduction

The Clinical WHO definition of the infertility is a “disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” (1). However, among 10 % infertile couples, exhaustive paraclinical investigations fail to find an identified etiology, leading to do a non –satisfying diagnosis of “unexplained infertility”(2). There’s no consensus concerning the tests to perform before concluding to an unexplained infertility (3). Laparoscopy isn’t systematically recommended unless an underlying tubal or pelvic pathology is suspected (4). Depending on the country, the recommended tests for exploring the etiologies of infertility are different. In UK, the standard fertility investigations include semen analysis, assessment of ovulation and tubal patency test (5). According to the American Society of Reproductive Medicine (ASRM), standard infertility evaluation includes semen analysis, assessment of ovulation by a measurement of progesterone concentration during the luteal phase, examination of the uterine cavity by an ultrasonography, an hysterosalpingogram and, if indicated, laparoscopy. Post coital test isn’t recommended (4). The NICE guidelines recommends semen analysis, measure of serum progesterone in the mid luteal phase to assess ovulation, and measure of gonadotrophins only for women with irregular cycles (6).Finally, most experts agree on the absolute necessity to have a sperm analysis, to check the integrity of the genital femal tractus, and to explore any disorder of ovulation. The evaluation of the ovarian reserve by FSH, AMH and sonographic count of antral follicles is discussed in first intention by physicians (5,6). Diagnosis laparoscopy is recommended only if a tubar pathology is suspected (5,7,8). Chlamydiae trachomatis serology isn’t recommended systematically (8).

In France, in 2016, 24 609 children are born after Assisted Reproductive Technologies (ART), representing about 3.1% of French live-births. More of 7 million children are born all

over the world after ART(3,9). Even in singletons, ART pregnancies have an increased risk of adverse obstetric and perinatal outcomes (9). However, ethiopathogeny of obstetrical complications is difficult to explain and it's difficult to distinguish the respective parts of ART and infertility. A lot of studies report a global increased risk of post-partum hemorrhage (PPH) (12). Concerning peripartum and postpartum outcomes, ART pregnancies were more exposed to cesarean sections, retained placenta, PPH and had a higher risk of failed induction of labor (13). In their meta-analysis, Qin et *al*. reported more pre-eclampsia, gestational diabetes mellitus (GDM), preterm births, small for age gestational age (SGA), cesarean sections, placenta previa,placental abruption, and ante per and post-partum hemorrhage in ART singleton pregnancies comparing to spontaneous pregnancies (14). Perinatal outcome seems to depend of the ART technique: more preterm birth and SGA newborns after fresh embryo transfer, more pre-eclampsia and large for gestational age newborns after frozen embryo transfer, more pre-eclampsia and SGA after oocyte donation (4). Some adverse maternal outcome seems related to some infertility etiologies. More birth-defects are described after ICSI with Testicular Sperm Extraction (TESE) spermatozoa (11,14,15). In their meta-analysis, Gasparri et *al.,* reported a higher rate of placenta previa after IVF in endometriosis women (17). In unexplained infertility, we could suppose that physicians just haven't found what they looked for! So, we wondered if there was an underlying unknown pathology that could maybe have an impact on the pregnancy outcome.

The objective of our study was to assay the obstetric outcome of ART pregnancies in women with unexplained infertility.

Material and methods.

We conducted a retrospective observational case - control cohort study between January 2011 and May 2017 in the ART Unit of our Department of Gynecology and Obstetrics. Infertility was defined as an absence of pregnancy after one year or more of regular

unprotected sexual intercourse. The infertility was considered as unexplained when the standard infertility investigations revealed no abnormalities. The tests performed on our study population were: evaluation of the ovarian reserve by a blood hormonal test at Day 2 or 3 of the cycle (Follicle Stimulating Hormone FSH, Luteinizing Hormone LH, Estradiol, Progesterone, Anti Mullerian Hormon AMH), a pelvic sonography for the count of antral follicles, a hysterosalpingography and a sperm assessment interpreted according to the OMS 2010 criterias.

The case group has included women with unexplained infertility and who obtained a pregnancy after ART. We talked about "unexplained" infertility only if sperm parameters and ovarian reserve were strictly normal. Even minor sperm abnormalities were considered as exclusion criterias for the diagnosis of unexplained infertility. Women with a suspicion of an underlying diminished ovarian reserve (FSH > 10 UI/L) were not included. Bologne criterias were used to define diminished ovarian reserve (18). Women over 40 years were not included, in order to avoid age-related infertility, which could be wrongly considered as "unexplained" infertility. The control group consisted of women who obtained a pregnancy after ART in a context of male infertility. For both groups, women were excluded if pregnancy was obtained spontaneously or after gamete donation.

Studied women were between 18 and 40 years old and were pregnant after intrauterine insemination (IUI) or In vitro fertilization (IVF) ~~or Intra cytoplasmic sperm injection IVF (ICSI IVF)~~ Concerning the ART strategy in case of unexplained infertility, two IUI cycles were performed in first line before IVF when woman was under than 38 years old, as previously published (19). IVF was performed in first line when women were older than 38. In control group, three IUI were proposed in first intention for moderate sperm abnormalities, with a total motile sperm count > 10^6 after sperm preparation. Under this threshold after sperm preparation, IVF was counselled in first line. ICSI was indicated : in second line for

unexplained infertility after IVF fertilization failure, in first line in case of severe sperm abnormalities (< 5 Million total motile sperm)

- Cases were matched to controls (2 controls for one case) for age, BMI, and smoking status . We used the WHO definition of the BMI to define the thinness (BMI <18 kg/m^2), a normal weight (18 kg/m^2 <BMI<25 kg/m^2), the overweight (25 kg/m^2 ≤BMI<30 kg/m^2) and the obesity (BMI ≥ 30 kg/m^2). For the tobacco consumption, we distinguished smoking women and not smoking women.

Studied parameters

Recorded data were: age, BMI, smoking status, AMH rate (ng/ml), counting of antral follicles determined by sonography. The outcomes that we studied for the first trimester were: early miscarriage (< 12 WG), vanishing twins (VT), ectopic pregnancy, and bleeding.

The outcomes of the 2nd and 3rd trimester assessed were: late miscarriage, preterm labor, placenta previa, placental abruption, premature rupture of membran (PROM), pre-eclampsia, intra uterine growth restriction (IUGR), GDM, gestational cholestasis, SGA. Concerning the childbirth and the neonatal outcomes, we collected gestational age at delivery, post-partum hemorrhage PPH), cesarean section, and birth weight.

Statistical analysis

Comparisons between groups and statistical analysis were performed using the SAS computer program, and t-test, Fisher's exact test, Chi-2 test, and Mann Withney test. Statistical significance was defined as $p<0.05$. Main outcome measure was obstetrical complications in singletons after 12 weeks' gestation. For the statistical analysis of obstetrical complications, we decided to analyze only singleton pregnancies. Indeed, twin pregnancies are well-known to have an increased risk of obstetrical outcome (20) and we did not want to induce a bias in the analysis of pregnancy outcome.

Ethic statement

This study was approved by the Ethical Committee of Aix-Marseille University (2018-18-10-003)

Results

We initially included 72 ART pregnancies (67 singletons and 5 twins) in Group A with unexplained infertility that have been matched with 149 ART pregnancies (129 singletons and 20 twins) in the control group B. Women were slightly older in the case group compared to the control group (group A: 31 ± 4.1 years *vs* group B (29.5 ± 4 years, p=0.003). We although found a significative minimal age difference between the two groups after exclusion of twins pregnancies. (group A: 31 ± 3.9 years vs group B 29.6 ± 3.9, p=0,011). The two groups did not differ for BMI (group A: 24.9 ± 5.7 vs group B : 24.7 ± 5.6 p=0.93), smoking status (group A : 32.9% vs group B : 31 %, p= 0.79), AMH rate and antral follicle count.

Pregnancy outcome are presented in table 2. No significant differences were observed for the rate of early miscarriage, ectopic pregnancy, VT and bleeding. Concerning the second and third trimester, the incidence of pre-eclampsia, GDM, placenta previa, and preterm labor was similar in both groups. Because of too few events in our study population, the risk of gestational cholestasis and placental abruption could not have been analyzed. Birth weight were similar in both groups (3187g ± 600g *Vs* 3140 g ± 610 g, p=0.6). Gestational age at delivery was similar (39 ± 3 weeks Vs 39 ± 2.5 weeks (p=0.78). We observed a non-significant increase of PPH in group A (6% vs 0.8%, OR=7, IC 0.79-64.3, p=0.08).

After exclusion of twins, we studied 67 singletons in the case group, matched with 129 singletons in the control group. Age, BMI and tobacco consumption were comparable between the two singleton groups. The incidence of the 1st trimester complications was comparable between the two groups, and also later for pre eclampsia, GDM, placenta praevia, and preterm labor. We found a non-significant increase of PPH (OR=5.5, IC 0.5-50, *p*=0.13) and SGA new-borns (OR=3.45, IC 0.65-18.1, *p*=0.14) in women with unexplained infertility.

Discussion

An increased risk of obstetrical complications is well established after ART pregnancies, even in singletons (14,19,20). The meta-analysis of Qin et *al.* that studied 161 370 ART singleton pregnancies, and reported a higher incidence of pre eclampsia, GDM, placenta previa, placental abruption, antepartum hemorrhage, PPH, polyhydramnios and oligoamnios, cesarean sections, preterm birth, low birth weight and SGA, perinatal mortality and congenital malformations.(14) Nagata et *al*., also reported an increased risk of placenta previa, placenta accreta, placental abruption, pre eclampsia, preterm birth and blood transfusion after IVF pregnancies (n = 3 147) comparing to spontaneous pregnancies. After ICSI, an increase of placental abruption was observed (23). Little is known for explaining poor ART obstetrical outcome and for distinguishing the own contributions of ART methods and infertility etiology. Depending to the etiology of the infertility, women seem to be exposed to different adverse outcomes. Fujii et *al.* observed more preterm labor and placenta previa in endometriosis women pregnant after ART, comparing to women who obtained a spontaneous pregnancy (24). Santulli et *al*. reported more early miscarriages in women with endometriosis (25).

For unexplained infertility, literature data report conflicting results. Kuivasaari-Pirinen et *al*. studied a cohort of 255 ART singleton pregnancies. Unexplained infertility was defined as infertility lasting at least one year for which no explanatory factor was identified after sonography, laparoscopy, laboratory paramaters and sperm analysis. An increase of SGA newborns and placental abruption was reported after ART pregnancy for unexplained infertility. The data were prospectively collected, and the maternal characteristics, the pregnancy and delivery informations were very extensive, which allowed an identification of confounding factors (26). In accordance, Pandian et *al.* studied 369 ART singleton pregnancies of women with unexplained infertility , and observed a higher incidence of

placental abruption, pre-term labor and pre-eclampsia comparing to spontaneous pregnancies. However, perinatal outcome was comparable, after adjusting on age and parity (27). Conversely, Isaksson et *al.* included 69 singletons ART pregnancies of women with unexplained infertility. The obstetrical outcome was comparable to other women who obtained an ART pregnancy for another medical indication (28).

The diagnosis of "unexplained" infertility isn't satisfactory both for couples and physicians. We could suspect an underlying etiology of infertility, without succeeding in highlighting what it could be. Some hypothesis are trying to explain "idiopathic" infertility. Some authors think that the zona pellucida of the oocyte could be "incompetent" and could impair the spermatozoa penetration inside, due to a genetic mutation of zona pellucida's glycoproteins (29). In a previous study (non published results, submitted), we observed similar fertilization rates in couples that underwent IVF for unexplained infertility, with only 4.6 % of fertilization failure. An endocrinological underlying cause could involve the leptin hormon. Leptin is considered as the satiety hormon. A higher leptin level has been observed in blood of women with unexplained infertily compared to a control group of fertile women, matched for BMI (27,28).Leptin could alter the steroidogenesis mechanisms, and thus the gamete maturation (32).Other research take an interest in endometrium's integrines. Some of them are necessary for the embryo implantation and for the placenta development. Dorostghoal et *al.* compared endometrium of fertile women to those of women with unexplained infertily. Expression of integrines was reduced in endometrium of infertile women , with an altered window of implantation (31).

In our study, we didn't observe a significant negative impact of a history of unexplained infertility on pregnancy outcome, compared to ART pregnancies for male infertility. The strength of our work is to have chosen restrictive inclusion criterias to define unexplained infertility. Women over 40 years were not included, in order to avoid age-related infertility,

that is considered sometimes wrongly as “unexplained” infertility and that could be a risk factor of adverse obstetrical outcome. Even minor sperm abnormalities were considered as exclusion criterias for the diagnosis of unexplained infertility. Our strict diagnosis criterias to define unexplained infertility explain our little cohort of cases. So – despite a small population included- we finally assessed an homogeneous study sample of women with a normal ovarian reserve without underlying pathology. The lack of significant results is maybe be due to a lack of puissance of the study. Another bias we can underline concerns the matching. We matched women on age, BMI, and tobacco status. In addition, the best methodology would have been to match also women on the ART technic to avoid bias due to that. Unfortunately, we didn’t have enough patients to compare four groups: unexplained infertility-IIU *Vs* Control group-IIU pregnancies and Unexplained infertility-IVF *Vs* Control group-IVF pregnancies. We agree that pregnancy outcome after unexplained infertility could be influenced by ART technique, and this hypothese needs a further study with a larger cohort.

No conflict of interest to disclose.

Author’s roles: M.A. and B.C. have conceived and designed the study. M.A, O.L., M.B. and B.C. made substantial contributions to acquisition, analysis and interpretation for data, in addition to drafting the article, reviewing the content and final manuscript approval. FB and AA revisited it critically and approved the final version to be submitted.

Figure and table legends.

Table 1: Obstetric outcome of ART pregnancies in women with unexplained infertility comparing to ART pregnancies in women pregnant after ART for male infertility. Women's characteristics.

Table 2: Obstetric outcome of ART singleton pregnancies in women with unexplained infertility comparing to ART singleton pregnancies in women pregnant after ART for male infertility. Statistic univarious study, matching 1 case for two controls.

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	Women with unexplained infertility (group A). N=72 cases	Women « healthy » treated for male infertility (group B). N=149 controls	p
Age (years)	31 ± 4.1	29.5 ± 4.0	0.003
BMI (kg/m2)	24.9 ±5.7	24.7 ±5.6	0.934
Smoking status (%)	23 (32.9)	45 (31)	0.79
AMH (ng/ml)	4.4 ± 3.1	3.8 ± 2.2	0.227
Antral folicle count	15.5 ± 9.5	15.3 ± 6.0	0.543
Type of ART :			<0.0001
IUI (%)	55 (76.4)	55 (36.9)	
IVF (%)	17 (23.6)	94 (63.1)	
Type of pregnancy			0.154
Singleton (%)	67 (93.1)	129 (86.6)	
Twins (%)	5 (6.9)	20 (13.4)	

Table 1 : Obstetric outcome of ART pregnancies in women with unexplained infertility comparing to ART pregnancies in women pregnant after ART for male infertility. Patient's characteristics

BMI: Body Mass Index ; AMH: Anti Mullerian Hormon ; IUI: Intra Uterine Insemination ; IVF: In Vitro Fertilization

Obstetric Outcome	Odds Ratio OR	CI	p
1st trimester bleeding	0.8	0.24-2.6	0.7
Early miscarriage	0.7	0.23-2.1	0.53
VT	2	0.12-31.9	0.6
Pre eclampsia	0.48	0.09-2.3	0.36
GDM	2.6	0.4-16	0.3
Placenta previa	1.7	0.23-12.2	0.6
Preterm labor	0.25	0.05-1.14	0.07
SGA	3.45	0.65-18.1	0.14
IUGR	0.55	0.06-5.4	0.6
PROM	0.3	0.35-2.7	0.29
Delivery	1.05	0.5-2.2	0.9
Cesarean section	1.02	0.5-2.1	0.95
PPH	5.5	0.5-50	0.13

Table 2: Obstetric outcome of ART singletons pregnancies in women with unexplained infertility comparing to ART singletons pregnancies in women treated for male infertility. Statistic univarious study, matching 1 case for two controls.

VT: Vanishing Twins; GDM : Gestational Diabetes Mellitus; SGA : Small for Gestational Age; IUGR : Intra Uterine Growth Restriction, PROM : Premature Rupture of Membran PPH: Post Partum Hemorrhage