



**HAL**  
open science

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

M. Amouyal, M. Boucekine, O. Paulmyer-Lacroix, A. Agostini, F. Bretelle, B. Courbiere

### ► To cite this version:

M. Amouyal, M. Boucekine, O. Paulmyer-Lacroix, A. Agostini, F. Bretelle, et al.. No specific adverse pregnancy outcome in singleton pregnancies after assisted reproductive technology (ART) for unexplained infertility. *Journal of Gynecology Obstetrics and Human Reproduction*, 2020, 49 (1), pp.101623. 10.1016/j.jogoh.2019.08.006 . hal-02479833

**HAL Id: hal-02479833**

**<https://amu.hal.science/hal-02479833v1>**

Submitted on 21 Jul 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

**No specific adverse pregnancy outcome in singleton pregnancies after Assisted  
Reproductive Technology (ART) for unexplained infertility.**

Amouyal M<sup>1</sup>, Boucekine M<sup>2</sup>, Paulmyer-Lacroix O<sup>1,3</sup>, Agostini A<sup>1</sup>, Bretelle F<sup>1,4</sup>, Courbiere  
B<sup>1,5</sup>

1 Departement of Gynecology-Obstetric and Reproductive Medicine, Hôpital La Conception /  
Hôpital Nord, AP-HM, Marseille, France

2 Aix-Marseille Univ, School of medicine - La Timone Medical Campus, EA 3279 CEReSS -  
Health Service Research and Quality of Life Center, |27 bd Jean Moulin cedex 05, F-13385,  
Marseille, France.

3 Aix Marseille Univ, Department of Histology-Embryology, Marseille, France

4 Aix Marseille Univ, UM 63, CNRS 7278, IRD 198, INSERM 1095, Marseille, France

5 Aix Marseille Univ, CNRS, IRD, Avignon Univ, IMBE UMR 7263, 13397, Marseille

**Corresponding author:**

Morgane Amouyal, - Departement of Gynecology-Obstetric and Reproductive Medicine, IVF  
Unit, Hôpital La Conception, 147 bd Baille, 13005 Marseille, France

morgane.amouyal@ap-hm.fr, Tel : 00 33 4 91 38 37 13

## **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 2<sup>nd</sup> and the 3<sup>rd</sup> 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 distinguish 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, etiopathogeny 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<sup>6</sup> 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 ( $\text{BMI} < 18 \text{ kg/m}^2$ ), a normal weight ( $18 \text{ kg/m}^2 < \text{BMI} < 25 \text{ kg/m}^2$  ), the overweight ( $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$  ) and the obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$  ). 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:  $31 \pm 4.1$  years vs group B ( $29.5 \pm 4$  years,  $p=0.003$ ). We although found a significant minimal age difference between the two groups after exclusion of twins pregnancies. (group A:  $31 \pm 3.9$  years vs group B  $29.6 \pm 3.9$ ,  $p=0.011$ ). The two groups did not differ for BMI (group A:  $24.9 \pm 5.7$  vs group B :  $24.7 \pm 5.6$   $p=0.93$ ), 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 ( $3187\text{g} \pm 600\text{g}$  Vs  $3140\text{g} \pm 610\text{g}$ ,  $p=0.6$ ). Gestational age at delivery was similar ( $39 \pm 3$  weeks Vs  $39 \pm 2.5$  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 1<sup>st</sup> 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 parameters 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 hormone. Leptin is considered as the satiety hormone. A higher leptin level has been observed in blood of women with unexplained infertility 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 infertility. 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.

## Références.

1. WHO | Infertility definitions and terminology [Internet]. WHO. [cité 4 avr 2019]. Disponible sur: <http://www.who.int/reproductivehealth/topics/infertility/definitions/en/>
2. Gelbaya TA, Potdar N, Jeve YB, Nardo LG. Definition and epidemiology of unexplained infertility. *Obstet Gynecol Surv.* févr 2014;69(2):109-15.
3. Agence de la biomédecine - Le rapport annuel médical et scientifique 2016 [Internet]. [cité 4 avr 2019]. Disponible sur: <https://www.agence-biomedecine.fr/annexes/bilan2016/donnees/sommaire-proc.htm>
4. Practice Committee of American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril.* août 2012;98(2):302-7.
5. Gelbaya TA, Potdar N, Jeve YB, Nardo LG. Definition and epidemiology of unexplained infertility. *Obstet Gynecol Surv.* févr 2014;69(2):109-15.
6. O'Flynn N. Assessment and treatment for people with fertility problems: NICE guideline. *Br J Gen Pract.* janv 2014;64(618):50-1.
7. Arrêté du 22 juin 2015 définissant les règles de bonnes pratiques applicables à la stimulation ovarienne y compris lorsqu'elle est mise en œuvre indépendamment d'une technique d'assistance médicale à la procréation | Legifrance [Internet]. [cité 4 avr 2019]. Disponible sur: <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=LEGITEXT000030834060&dateTexte=20180910>
8. Collège National des Gynécologues et Obstétriciens Français. *Journal de Gynécologie Obstétrique et Biologie de la Reproduction* [Internet]. sept 2005 [cité 4 avr 2019];34(5):513. Disponible sur: <https://linkinghub.elsevier.com/retrieve/pii/S0368231505828674>
9. Boujenah J, Montforte M, Hugues JN, Sifer C, Poncelet C. [Laparoscopy in ART?]. *Gynecol Obstet Fertil.* sept 2015;43(9):604-11.
10. Mansour R, Ishihara O, Adamson GD, Dyer S, de Mouzon J, Nygren KG, et al. International Committee for Monitoring Assisted Reproductive Technologies world report: Assisted Reproductive Technology 2006. *Hum Reprod.* juill 2014;29(7):1536-51.
11. Stern JE, Gopal D, Diop H, Missmer SA, Coddington CC, Luke B. Inpatient hospitalizations in women with and without assisted reproductive technology live birth. *J Assist Reprod Genet.* août 2017;34(8):1043-9.
12. Fauser BCJM, Devroey P, Diedrich K, Balaban B, Bonduelle M, Delemarre-van de Waal HA, et al. Health outcomes of children born after IVF/ICSI: a review of current expert opinion and literature. *Reprod Biomed Online.* févr 2014;28(2):162-82.
13. Vannuccini S, Clifton VL, Fraser IS, Taylor HS, Critchley H, Giudice LC, et al. Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome. *Hum Reprod Update.* févr 2016;22(1):104-15.

14. Qin J, Liu X, Sheng X, Wang H, Gao S. Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: a meta-analysis of cohort studies. *Fertil Steril.* janv 2016;105(1):73-85.e1-6.
15. Esteves SC, Roque M, Bradley CK, Garrido N. Reproductive outcomes of testicular versus ejaculated sperm for intracytoplasmic sperm injection among men with high levels of DNA fragmentation in semen: systematic review and meta-analysis. *Fertil Steril.* 2017;108(3):456-467.e1.
16. Kawwass JF, Kulkarni AD, Hipp HS, Crawford S, Kissin DM, Jamieson DJ. Extremities of body mass index and their association with pregnancy outcomes in women undergoing in vitro fertilization in the United States. *Fertil Steril.* déc 2016;106(7):1742-50.
17. Gasparri ML, Nirgianakis K, Taghavi K, Papadia A, Mueller MD. Placenta previa and placental abruption after assisted reproductive technology in patients with endometriosis: a systematic review and meta-analysis. *Arch Gynecol Obstet.* juill 2018;298(1):27-34.
18. Busnelli A, Papaleo E, Del Prato D, La Vecchia I, Iachini E, Paffoni A, et al. A retrospective evaluation of prognosis and cost-effectiveness of IVF in poor responders according to the Bologna criteria. *Hum Reprod.* févr 2015;30(2):315-22.
19. Ohannessian A, Loundou A, Gnisci A, Paulmyer-Lacroix O, Perrin J, Courbiere B. Unexplained infertility: live-birth's prognostic factors to determine the ART management. *Minerva Ginecol.* déc 2017;69(6):526-32.
20. Santana DS, Surita FG, Cecatti JG. Multiple Pregnancy: Epidemiology and Association with Maternal and Perinatal Morbidity. *Rev Bras Ginecol Obstet.* sept 2018;40(9):554-62.
21. Allen VM, Wilson RD, Cheung A, GENETICS COMMITTEE, REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY COMMITTEE. Pregnancy outcomes after assisted reproductive technology. *J Obstet Gynaecol Can.* mars 2006;28(3):220-33.
22. Okun N, Sierra S, GENETICS COMMITTEE, SPECIAL CONTRIBUTORS. Pregnancy outcomes after assisted human reproduction. *J Obstet Gynaecol Can.* janv 2014;36(1):64-83.
23. Nagata C, Yang L, Yamamoto-Hanada K, Mezawa H, Ayabe T, Ishizuka K, et al. Complications and adverse outcomes in pregnancy and childbirth among women who conceived by assisted reproductive technologies: a nationwide birth cohort study of Japan environment and children's study. *BMC Pregnancy Childbirth.* 20 févr 2019;19(1):77.
24. Fujii T, Wada-Hiraike O, Nagamatsu T, Harada M, Hirata T, Koga K, et al. Assisted reproductive technology pregnancy complications are significantly associated with endometriosis severity before conception: a retrospective cohort study. *Reprod Biol Endocrinol.* 3 nov 2016;14(1):73.

25. Santulli P, Collinet P, Fritel X, Canis M, d'Argent EM, Chauffour C, et al. [Management of assisted reproductive technology (ART) in case of endometriosis related infertility: CNGOF-HAS Endometriosis Guidelines]. *Gynecol Obstet Fertil Senol.* mars 2018;46(3):373-5.
26. Kuivasaari-Pirinen P, Raatikainen K, Hippeläinen M, Heinonen S. Adverse Outcomes of IVF/ICSI Pregnancies Vary Depending on Aetiology of Infertility. *ISRN Obstet Gynecol.* 2012;2012:451915.
27. Pandian Z, Bhattacharya S, Templeton A. Review of unexplained infertility and obstetric outcome: a 10 year review. *Hum Reprod.* déc 2001;16(12):2593-7.
28. Isaksson R, Gissler M, Tiitinen A. Obstetric outcome among women with unexplained infertility after IVF: a matched case-control study. *Hum Reprod.* juill 2002;17(7):1755-61.
29. Paz G, Yavetz H, Margalit M, Hevlin-Schwartz T, Amit A. [The involvement of the zona pellucida in unexplained infertile women]. *Harefuah.* janv 2008;147(1):77-80, 93, 92.
30. Tafvizi F, Masomi M. Comparison of Serum Leptin Level in Women with Unexplained Infertility and Fertile Women in Iran. *J Obstet Gynaecol India.* oct 2016;66(Suppl 1):466-70.
31. Kumari P, Jaiswar SP, Shankhwar P, Deo S, Ahmad K, Iqbal B, et al. Leptin as a Predictive Marker in Unexplained Infertility in North Indian Population. *J Clin Diagn Res.* mars 2017;11(3):QC28-31.
32. Smith GD, Jackson LM, Foster DL. Leptin regulation of reproductive function and fertility. *Theriogenology.* 1 janv 2002;57(1):73-86.
33. Dorostghoal M, Ghaffari H-O-A, Shahbazian N, Mirani M. Endometrial expression of  $\beta 3$  integrin, calcitonin and plexin-B1 in the window of implantation in women with unexplained infertility. *Int J Reprod Biomed (Yazd).* janv 2017;15(1):33-40.

	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/m <sup>2</sup> )	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 follicle count	15.5 ± 9.5	15.3 ± 6.0	0.543
Type of ART :			
IUI (%)	55 (76.4)	55 (36.9)	<0.0001
IVF (%)	17 (23.6)	94 (63.1)	
Type of pregnancy			
Singleton (%)	67 (93.1)	129 (86.6)	0.154
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