Poor response in ART is associated with pregnancy complications

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Abstract

Introduction: It is generally accepted that obstetric and perinatal complications such as gestational diabetes, preeclampsia and IUGR are more common in older women. The results of studies that investigated this issue were inconclusive. The term "poor responder" refers to patients with diminished ovarian reserve, usually older women. Our study aimed to study whether there is an association between poor ovarian response in artificial reproductive technology and pregnancy complications.

Material and methods: Retrospective, case-control study, at a tertiary, university-affiliated IVF centre, from 2011 to 2017. Patients who conceived and delivered after ART treatment were analysed. 75 poor responders (≤3 oocytes retrieved) after stimulation with gonadotropins (study group) were matched by day of ovum pick-up (OPU) to 75 normo-responders (≥4 oocytes retrieved). Main outcome measures were incidence of preeclampsia, gestational diabetes mellitus (GDM) and neonatal birth weight.

Results: There were no significant differences in maternal age, gravidity, parity, BMI, gestational age at delivery, mode of delivery and Apgar score between groups. Poor responders had higher incidence of GDM (27% compared to 6.8%, P=0.001) and of intrauterine growth restriction (IUGR) (13.5% compared to 4.1%, P=0.04) than did normo-responders. Although poor responder patients experienced higher incidence of preeclampsia (8.1% compared to 5.4%), this did not achieve statistically significance (P=0.74). Poor responders with GDM were of similar age (34.6 ± 5.6 vs. 34.4 ± 5.1, P=0.8) and BMI (27.8 ± 6 vs. 24.8 ± 5.4, P=0.06) as poor responders without GDM. However, normo-responders with GDM were older (34.6 ± 3.7 vs. 32.4 ± 5.8, P=0.01) and had higher BMI (29.5 ± 0.6 vs. 22.9 ± 4.7, P=0.008) than normo-responders without GDM.

Conclusions: Poor responders had higher incidence of GDM and IUGR compared to women with normal ovarian response. Poor response in ART is an independent risk factor for GDM and IUGR. This finding may have wider implications on the mother and the fetus, and appropriate counselling should be considered.

Abrreviations: ART- Artificial Reproductive Technology, IVF- In Vitro Fertilization, GDM- Gestational Diabetes Mellitus, IUGR- Intrauterine Growth Restriction, BMI- Body Mass Index.

Introduction

The term "poor responder" refers to patients with diminished ovarian reserve, usually with lower success rates in IVF. It is very important to identify poor responders in order to select the appropriate protocol for maximizing ovarian response and when counseling patients. However, there is no standard definition of a poor responder [1,2].

Two recent studies based on large clinical databases confirmed that the threshold of three oocytes adopted by the ESHRE consensus is adequate to identify patients with a lower likelihood of achieving a live birth [3,4]. Approximately 10% of women seeking fertility treatment fit this definition; very often, older patients presenting with low ovarian reserve.

It is generally accepted that obstetric and perinatal complications such as gestational diabetes, preeclampsia and IUGR are more common in older women. Whether this is due to the general aging process or due to the aging of the ovary and the ovum, is not known. The results of studies that investigated this issue were inconclusive [5-9].

The current study aimed to determine whether pregnancies achieved after ART in women with poor ovarian response are at increased risk for these complications.

Materials and methods

This retrospective, case-control study was conducted at Meir Medical Center from 2011 to 2017. Poor response was defined as the retrieval of no more than 3 oocytes at follicle aspiration, after controlled ovarian stimulation with high-dose gonadotropins (300 IU daily or more).

Pregnant women 20-43 years of age were included. Of these, 75 (study group) who conceived after a poor ovarian response were matched with 75 pregnancies (control group) from normal ovarian responders (retrieval of more than 3 oocytes). In order to avoid bias due to possible differences in oocyte growth media and laboratory staff,

controls were matched based on the same ovum pickup day. We did not include cancelled cycles or those with insufficient follicular growth that yielded no oocytes after pickup.

In order to avoid the possible bias of large for gestational age infants of blastocyst embryo transfer [10], we included only day 3, fresh embryo transfers. Data regarding ART cycles and established pregnancies and deliveries were obtained from our electronic database. Each woman was only included once.

Exclusion criteria were multiple pregnancies including vanishing twin, ectopic and heterotopic pregnancies or pregnancies ending in spontaneous abortion. Patients with chronic disease before conception (diabetes mellitus, hypertension, kidney disease, liver disease, malignancy, or autoimmune disease) were excluded, as well.

Primary end points included the incidence of pregnancy-related disorders, including preeclampsia (PET), gestational diabetes mellitus (GDM) and intrauterine growth restriction (IUGR). PET was defined based on ACOG criteria, as new onset of systolic blood pressure ≥140 mmHg or ≥90 mmHg diastolic on 2 occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure, and proteinuria ≥300 mg per 24 hour urine collection [11].

GDM was defined as an abnormal glucose tolerance test result between 24 and 28 weeks of gestation [12]. IUGR was defined as birth weight below the 10th percentile for gestational age [13]. Secondary end points were the duration of pregnancy, mode of delivery and 1 and 5-minute Apgar scores.

The study was approved by institutional ethics review board.

Data analysis

Statistical analysis was done using SPSS-25 (IBM, Armonk,NY). Statistical significance between two groups was calculated using the Chi-square test or Fisher's exact test for differences in qualitative variables and t-test or Mann-Whitney for continuous variables, each when appropriate. Logistic regression analysis was done to examine whether the analyzed variables had an independent influence. $P<0.05$ was the critical point for statistical difference.

Results

A total of 150 patients were included: 75 poor responders were compared to 75 normo-responders. There were no significant differences in maternal age, gravidity, parity and maternal BMI between the groups. FSH levels (on day 3 of menstrual cycle) were higher in poor responders as compared to normo-responders (10.2 ± 6.5 vs. 7.48 ± 3.04, P=0.0001). FSH to LH ratio was higher in poor responders compared to normo-responders (2.3 ± 1.19 Vs. 1.5 ± 2.29, P=0.0001). Poor responders had significantly lower antral follicular count (AFC) (7 ± 3) compared with the control group (Table 1). Poor responders needed significantly higher amount of gonadotropins per cycle (3405 ± 1400 vs. 1949 ± 860, P=0.0001; Table 1). The use of ICSI was similar between the groups (P=0.08). Poor responders did significantly more IVF attempts when compared with controls (3.8 ± 2.8 vs.1.5 ± 1.6. P=0.001).

There was no difference in gestational age at delivery, mode of delivery, birthweight (excluding cases with intrauterine growth restriction) and Apgar score between groups (Table 2).

Poor responders had higher incidence of GDM (27% vs. 6.8%, P=0.001). We did not checked for Insulin resistance however there were no statistical significant differences in fasting glucose nor in the Glycated Hemoglobin (Hgb A1c) levels between the groups (Table 1).

Poor responders with GDM were of comparable age (34.6 ± 5.6 vs. 34.4 ± 5.1 years, P=0.8) and BMI (27.8 ± 6 vs. 24.8 ± 5.4, P=0.06) as poor responders without GDM. However, normo-responders who had GDM were older (34.6 ± 3.7 vs. 32.4 ± 5.8, P=0.01) and had higher BMI (29.5 ± 0.6 vs. 22.9 ± 4.7, P=0.008) than normo-responders without GDM. Preeclampsia was noted more frequently among poor responders (8.1% vs. 5.4%), however the difference did not reach statistical significance (Table 3).

We found higher incidence of IUGR (13.5% vs. 4.1%, P=0.04) among poor responders. Logistic regression analysis showed OR of 5.6 and 5.2 for GDM and IUGR, respectively (p=0.003, 0.038).

Discussion

The impact of the ageing ovary and oocytes on pregnancy complications has not been investigated thoroughly and the results of studies who evaluated this topic were inconclusive [6,7].

Gestational diabetes mellitus is associated with the insulin resistance which is mediated primarily by placental secretions of diabetogenic hormones. It is more common in older and in overweight women. The incidence of GDM varies between 1.4% and 14% depending on the characteristics of the population studied and on the screening method [14].

As opposed to the control group which had comparable rate of GDM as the general population (8%), poor responders had significantly higher incidence of gestational diabetes (27%). An interesting finding is that poor responders with GDM were of comparable age and BMI as poor responders without GDM. However, normo-responders with GDM resembled the general population, being older with higher BMI.

Table 1. Patient's characteristics

Characteristic	Poor responders	Normo-responders	P-value
Age, years	34.5±5.2	32.5±5.7	0.06
BMI	25.6±5.7	23.4±4.9	0.08
Gravidity	2.3±1.8	1.8±1.27	0.06
Parity	0.7±0.69	0.45±0.74	0.079
FSH (mean±SD)*	10.2±6.5	7.5±3.04	0.0001
FSH/LH ratio*	2.3±1.19	1.5±2.29	0.0001

*Measured on day 3 of the menstrual cycle

Table 2. Infant characteristics

Characteristic	Poor responders	Normo-responders	P-value
Birth weight, g (mean ± SD)*	3097 ± 587	3013 ± 644	0.54
Gestational age at delivery, weeks (mean ± SD)	38 ± 2.2	38.4 ± 2.8	0.27
Apgar 1 minute (mean ± SD)	8.6 ± 1.2	8.7 ± 0.93	0.68
Apgar 5 minutes (mean ± SD)	9.8 ± 0.6	9.9 ± 0.34	0.11

*Excluding cases with intrauterine growth restriction.
SD-standard deviation

Table 3. Obstetric complications

Variable	Poor responders (N=75)	Normo-responders (N=75)	P-value
Gestational diabetes mellitus	20 (27%)	5 (6.8%)	0.001
Intrauterine growth restriction	10 (13.5%)	3 (4.1%)	0.04
Preeclampsia	6 (8.1%)	4 (5.4%)	0.74

This implies that the etiology of GDM among poor responders is different and might be related to older biological age of poor responders. Isik et al, reported a lower ovarian reserve in type 2 diabetic patients compared with healthy controls (Isik et al., 2012).

A possible explanation for lower pregnancy rates in poor responders is not only fewer oocytes, but also impaired quality. Muller-Hocer et al. reported of mitochondrial alterations (i.e. swelling, vacuolization and cristae alterations) with increasing age [15]. The free radical theory of ageing remains a leading hypothesis to explain the deterioration of oocytes and their mitochondrial function [15,16]. Intra-ovarian reactive oxygen species increase with aging. This results in oxidative stress and declines in oocyte quality and in IVF and pregnancy success rates [14]. We can postulate that similar changes are present in the oocytes of younger patients with low ovarian reserve, a phenomenon known as biological aging [16-19].

IUGR and PET are consequences of placental insufficiency. Mitochondria, as cell energy producers, are potentially associated with the pathogenesis of placental insufficiency. Impaired mitochondrial function and number may explain the oxygen and nutrient restriction, as well as oxidative stress, seen in these patients [17-19].

The relation between mitochondrial damage in aging oocytes and increased demand for oxygen might explain the higher rates of IUGR and PET among poor responders.

To conclude, poor ovarian response is not only a descriptive term related to gonadotropin stimulus but may have a wider implication on the mother and the fetus; thus, appropriate counseling should be considered.

Tweetable abstract

Poor response in ART is an independent risk factor for gestational diabetes mellitus and intrauterine growth restriction and is not related to older maternal age or higher body mass index. Thus, poor ovarian response may have wide implications on the mother and the fetus, therefore appropriate counseling should be considered.

Conflicts of interest

There is no conflict of interest.

Funding information

References

1. Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G, et al. (2011) ESHRE consensus on the definition of 'poor response to ovarian stimulation for in vitro fertilization: The Bologna criteria. *Hum Reprod* 26: 1616-1624.

2. Gonda KJ, Domar AD, Gleicher N, Marrs RP (2018) Insights from clinical experience in treating IVF poor responders. *Reprod Biomed Online* 36: 12-19. [Crossref]

3. Bhattacharya S, Maheshwari A, Mollison J (2013) Factors associated with failed treatment: An analysis of 121,744 women embarking on their first IVF Cycles. *PLoS One* 8: 1-13. [Crossref]

4. Polyzos NP, Nwoye M, Corona R, Blockeel C, Stoop D, et al. (2014) Live birth rates in Bologna poor responders treated with ovarian stimulation for IVF/ICSI. *Reprod Biomed Online* 28: 469-474. [Crossref]

5. Maman E, Lunenfeld E, Levy A, Hilel Vardi GP (1998) Obstetric outcome of singleton pregnancies conceived by in vitro fertilization and ovulation induction compared with those conceived spontaneously. *Fertil Steril* 70: 240-245.

6. Parlakgümüş HA, Haydardedeoğlu B, Simşek E, Cok T, Yalçınkaya C, et al. (2011) Are pregnancy complications increased in poor responders? *J Turkish Ger Gynecol Assoc* 12: 1-3. [Crossref]

7. Shand AW, Whitton K, Pasfield A, Nassar N, McShane M, et al. (2014) Evaluation of anti-Mullerian hormone in the first trimester as a predictor for hypertensive disorders of pregnancy and other adverse pregnancy outcomes. *Aust New Zeal J Obstet Gynaecol* 54: 244-249. [Crossref]

8. Shevell T, Malone FD, Vidaver J, Porter TF, Luthy DA, et al. (2005) Assisted reproductive technology and pregnancy outcome. *Obstet Gynecol* 106: 1039-1045.

9. van Disseldorp J, Eijkemans R, Fauser B, Broekmans F (2010) Hypertensive pregnancy complications in poor and normal responders after in vitro fertilization. *Fertil Steril* 93: 652-657.

10. Zhu J, Lin S, Li M, Chen L, Lian Y, et al. (2014) Effect of in vitro culture period on birthweight of singleton newborns. *Hum Reprod* 29: 448-454. [Crossref]

11. Roberts James M, Druzin Maurice, August Phyllis A, Gaiser Robert R, Bakris George, et al. (2013) Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 122: 1122-1131. [Crossref]

12. Baz B, Riveline JP, Gautier JF (2016) Endocrinology of pregnancy: Gestational diabetes mellitus: definition, aetiological and clinical aspects. *Eauropian J Endocrinol* 174: 43-51. [Crossref]

13. Gordijn SJ, Beune IM, Ganzevoort W (2018) Building consensus and standards in fetal growth restriction studies. *Best Pract Res Clin Obstet Gynaecol* 49: 117-126. [Crossref]

14. Kim C, Dunn RL, Braffett B, Cleary PA, Arends V, et al. (2016) Ovarian reserve in women with Type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabet Med* 33: 691-692. [Crossref]

15. Müller-Höcker J, Schäfer S, Weis S, Münscher C, Strowitzki T (1996) Morphological-cytochemical and molecular genetic analyses of mitochondria in isolated human oocytes in the reproductive age. *Mol Hum Reprod* 2: 951-958. [Crossref]

16. Mihalas BP, Redgrove KA, McLaughlin EA, Nixon B (2017) Molecular mechanisms responsible for increased vulnerability of the ageing oocyte to oxidative damage. *Oxid Med Cell Longev* 2017: 4015874. [Crossref]

17. Lefebvre T, Roche O, Seegers V, Cherif M, Khiati S, et al. (2018) Study of mitochondrial function in placental insufficiency. *Placenta* 67: 1-7. [Crossref]

18. May-Panloup P, Boucret L, de la Barca JMC, Desquiret-Dumas V, Ferré-L'Hotellier V, et al. (2016) Ovarian ageing: The role of mitochondria in oocytes and follicles. *Hum Reprod Update* 22: 725-743. [Crossref]

19. Novielli C, Mandò C, Tabano S, Anelli GM, Fontana L, et al. (2017) Mitochondrial DNA content and methylation in fetal cord blood of pregnancies with placental insufficiency. *Placenta* 55: 63-70. [Crossref]