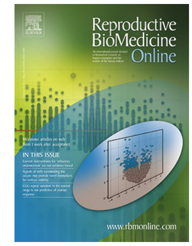
Reproductive BioMedicine Online (2016) **32**, 532–537

www.sciencedirect.com
www.rbmonline.com



ARTICLE

Younger poor ovarian response women achieved better pregnancy results in the first three IVF cycles

Yajuan Yang [a,b,c], Xiuhua Sun [d], Linlin Cui [a,b,c], Yan Sheng [a,b,c], Rong Tang [a,b,c], Daimin Wei [a,b,c], Yingying Qin [a,b,c], Weiping Li [e,*], Zi-Jiang Chen [a,b,c,f,*]

[a] *Center for Reproductive Medicine, Provincial Hospital Affiliated to Shandong University, Jinan 250001, China;* [b] *The Key laboratory for Reproductive Endocrinology of Ministry of Education, China;* [c] *Shandong Provincial Key Laboratory of Reproductive Medicine, Jinan 250001, China;* [d] *Department of Obstetrics, Qingdao Municipal Hospital, Qingdao 266011, China;* [e] *Department of Obstetrics and Gynecology, Renji Hospital affiliated to Shanghai Jiaotong University, Shanghai 200127, China;* [f] *National Research Center for Assisted Reproductive Technology and Reproductive Genetics, Jinan 250001, China*

* Corresponding authors. *E-mail addresses:* liweiping@smhb.gov.ch (W Li); chenzijiang@hotmail.com (Z-J Chen).

Dr Yajuan Yang will receive her MD from the School of Medicine Shandong University, Shandong, China in 2016. She is now receiving her clinical training at the Center for Reproductive Medicine of Shandong University, which is one of the largest IVF centres in China and is a pioneer in IVF, oocyte cryopreservation and reproductive endocrinology and genetic diseases. She is especially interested in reproductive endocrinology, premature ovarian insufficiency and poor ovarian response.

Abstract This retrospective cohort study observed the live birth rates as well as cumulative live birth rates in women with poor ovarian response (POR) undergoing IVF–embryo transfer treatment, stratified for age and cycle number. Four hundred and one patients with POR diagnosed according to the Bologna criteria were enrolled and 700 IVF–ET cycles were analysed. The overall live-birth rate per cycle was 18.3%. From cycle 1 up to cycle 3, the live-birth rates decreased significantly from 22.2% to 11.1%. The live-birth rate fell to 2.4% in cycles 4 and over. When age advanced, the live birth rates decreased obviously ($P < 0.01$): 30.0% for women <35 years old, 17.0% for those 35–40 years old, and 9.0% for women older than 40 years. Similarly, the cumulative live birth rates dropped from 48.0% (<35 years) to 16.9% (≥40 years) accordingly. Younger patients (<35 years old) with POR achieved better pregnancy results compared with patients of advanced age. Extremely low live-birth rates could be anticipated after three unsuccessful cycles; therefore it may not be appropriate to suggest more IVF cycles in POR women.

KEYWORDS: Bologna criteria, cumulative live birth rate, live birth rate, poor ovarian responder, poor ovarian response

http://dx.doi.org/10.1016/j.rbmo.2016.02.013
1472-6483/

Introduction

Since the first report of a woman who manifested a peak value of oestrogen <300 pg/ml during ovarian stimulation in 1983 (Garcia et al., 1983), poor ovarian response (POR) has become a major challenge for clinicians. The prevalence of POR ranges from 9% to 24% in IVF treatment (Ubaldi et al., 2005). Although different protocols and adjuvants for ovarian stimulation have been proposed to improve ovarian response, it seems that patients with POR benefit little from the interventions (Pandian et al., 2010; Venetis et al., 2010). Furthermore, disagreement on the definition of POR limited the comparison and generalization of results from different clinical trials until the Bologna consensus was published in 2011 (Ferraretti et al., 2011; Polyzos and Devroey, 2011). Poor pregnancy results, such as live-birth rate (LBR) per cycle being less than 10% and varying from 2.6% to 8.3%, similarly, and LBR per woman varying from 7.4% to 20.5%, have been reported (Busnelli et al., 2015; Ke et al., 2013; La Marca et al., 2015; Polyzos et al., 2012, 2014). However, few comparative data about LBR and cumulative live-birth rate (CLBR) in repeated cycles have been published until now. CLBR instead of LBR per cycle provides a reference for continued treatment for individual patients.

It has been established that both LBR and CLBR decline with increasing maternal age for an infertile population (Luke et al., 2012; Malizia et al., 2009; Stern et al., 2010). According to previously published reviews applying different diagnostic criteria for POR, young patients established more pregnancies compared with older patients with POR (Oudendijk et al., 2012). However, in most studies using Bologna criteria, no association between age and LBR has been revealed (Polyzos et al., 2012, 2014, 2015).

The aim of the present study was to observe the LBR and CLBR in 401 patients with POR diagnosed according to the Bologna criteria, undergoing consecutive cycles of IVF/intracytoplasmic sperm injection (IVF/ICSI)–embryo transfer, and compare the pregnancy results among different age and after multiple treatment cycles.

Materials and methods

This research was approved by Institutional Review Board of Reproductive Medicine of Shandong University on 29 October 2015 (IRB reference number 1827). Four hundred and one women with POR diagnosed according to the Bologna criteria (Ferraretti et al., 2011) were enrolled, and underwent their first IVF/ICSI–embryo transfer treatment cycles from January to December of 2013 in the Reproductive Hospital Affiliated to Shandong University. All consecutive cycles were followed. The Bologna criteria were applied as follows.

At least two of the three features should be present: (i) advanced maternal age (≥40 years) or any other risk factors for POR (previous ovarian surgery, ovarian endometrioma, genetic abnormalities for POR, previous chemotherapy); (ii) a previous POR (≤3 oocytes retrieved with a conventional stimulation protocol using at least 150 IU gonadotrophin for initiation); and (iii) an abnormal ovarian reserve test (i.e. antral follicle count (AFC) <5 follicles or anti-Müllerian hormone (AMH) <1.1 ng/ml).

Two episodes of ≤3 oocytes retrieved with a conventional stimulation protocol in the absence of advanced maternal age (≥40 years) and abnormal ovarian reserve tests were also included. Patients ($n = 7$) were excluded if they pursued treatment for preimplantation genetic diagnosis or screening (PGD/PGS). Patients ($n = 10$) with remaining embryos cryopreserved for transfer were removed.

Different ovarian stimulation protocols were applied in this study and included: gonadotrophin-releasing hormone (GnRH) agonist short protocol, GnRH agonist long protocol, natural cycle, microdose flare-up protocol, GnRH antagonist protocol, and ultra-long protocol (Kahraman et al., 2009; La Marca et al., 2015; Polyzos et al., 2012; Sunkara et al., 2014). During ovarian stimulation for women showing poor response adjustments, including high dose of gonadotrophin for initiation and prolonged stimulating period, were made. No adjuvants such as dehydroepiandrosterone, growth hormone, testosterone or melatonin were used during treatments.

Outcome measures

LBR per cycle, LBR per woman, and CLBR were calculated. Live birth was defined as the delivery of at least one liveborn infant after ≥28 weeks' gestation. Both fresh and frozen embryo transfers were included to calculate cumulative live birth.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) for continuous variables following normal distribution, median (interquartile range) for continuous variables following nonnormal distribution, and the numbers (percentage) for categorical variables. Comparisons of LBR and CLBR among different groups were performed using the chi-squared test and Fisher's exact test. Multivariable logistic regression analysis was performed to identify potential factors contributing to live birth. SPSS version 19.0 (Armonk, NY, IBM Corp.) was used for analysis. The two-tailed value of $P < 0.05$ was considered statistically significant. P-value was corrected according to Bonferroni adjustment when making multiple comparisons among groups.

Results

The overall LBR per cycle was 18.3% in the 401 women undergoing 700 cycles of IVF/ICSI–embryo transfer. The CLBR per woman was 31.9%. The protocols for ovarian stimulation included: GnRH agonist short protocol ($n = 495$), GnRH agonist long protocol ($n = 83$), natural cycle ($n = 56$), microdose flare-up protocol ($n = 36$), GnRH antagonist protocol ($n = 21$), and ultra-long protocol ($n = 9$). The median number (interquartile range) of oocytes retrieved was 3 (2–5). The median number (interquartile range) of embryos obtained per cycle was 2.0 (1.0–2.0). Considering different ovarian stimulation protocols may affect the outcome of IVF, multivariable logistic regression analysis has been performed and no association between ovarian stimulation protocols and LBR was revealed.

Table 1 Clinical characteristics of patients with poor ovarian response ($n = 401$).

Characteristics	*Data*
Age (years)[a]	37 (32–40)
BMI (kg/m^2)[b]	23.82 ± 3.42
Duration of infertility (years)[a]	4 (2–8)
Nulliparity[c], *n* (%)	148 (36.9)
Basal serum FSH (IU/ml)[a]	8.17 (6.80–10.40)
Bilateral AFC[a]	7 (5–9)
AMH (ng/ml)[a]	0.57 (0.29–0.86)
Causes of infertility[c]	
Tubal factor, *n* (%)	289 (72.1)
Male factor, *n* (%)	52 (13.0)
Endometriosis, *n* (%)	34 (8.5)
Unexplained, *n* (%)	21 (5.2)
Oligo-/anovulation, *n* (%)	5 (1.2)
Risk factors for POR[c]	
Age ≥40 years, *n* (%)	148 (36.9)
Ovarian endometriomas, *n* (%)	31 (7.7)
Ovarian surgery, *n* (%)	92 (22.9)
X chromosome abnormality[d], *n* (%)	1 (0.2)
AMH <1.1 ng/ml, *n* (%)	360 (89.8)
Bilateral AFC <5, *n* (%)	64 (16.0)

AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; POR = poor ovarian response.
[a]Data were expressed as median (interquartile range) for continuous variables not normally distributed.
[b]Data were expressed as mean ± SD for continuous variables normally distributed.
[c]Data were expressed as the numbers (percentage) for categorical variables.
[d]Karyotype 47, XXX.

The clinical characteristics of all participants are presented in Table 1. Among them, 148 (36.9%) women were over 40 years old, and 92 patients (22.9%) had a history of ovarian surgery, including ovarian cystectomy (n = 37), excision of ovarian endometriomas (n = 31), excision of ovarian teratoma (n = 12), laparoscopic bilateral ovarian drilling (n = 5), unilateral oophorectomy (n = 5), ovarian repair of corpus luteum cyst rupture (n = 1), excision of ovarian abscess (n = 1).

Table 2 shows the LBR and CLBR. From cycle 1 to cycle 3, the LBR per cycle decreased significantly ($P < 0.01$), from 22.2% in the first cycle to 11.1% in the third cycle. The CLBR increased from 22.2% to 31.7% accordingly. Extremely low LBR (2.4%) was obtained in patients with four consecutive cycles or more.

The LBR and CLBR stratified by age are shown in Table 3. Age was divided into three groups and different LBR were observed; i.e. 30.0% for women younger than 35 years of age, 17.0% for those aged 35–40 years, and 9.0% for women exceeding 40 years of age ($P < 0.01$). The CLBR was significantly higher for young patients aged <35 years (48.0%), compared with 30.1% for those aged 35–39 years, and 16.9% for women exceeding 40 years of age ($P < 0.01$). In the first cycle, younger patients (i.e. < 35 years old) showed higher LBR (36.0%) compared with older women (i.e. 19.4% for 35–40 years old and 10.1% for ≥40 years old) ($P < 0.01$). However, these differences between young and old patients disappeared among the third and subsequent treatment cycles.

Multivariable logistic regression analysis showed that age and ovarian surgery history are associated with the LBR. The OR for live birth were 0.90 (95%CI: 0.86–0.94) and 2.22 (95%CI: 1.34–3.70), respectively.

Discussion

The present study compared the LBR and CLBR in patients with POR fulfilling the Bologna criteria among IVF/ICSI cycles and at different ages. A low but reasonable CLBR (31.9%) was observed, especially for patients younger than 35 years old (48.0%). The majority of live births (99.2%) were achieved during the first three cycles.

The only study reporting CLBR for patients with POR, according to the Bologna criteria, was published by Ke H et al., who reported CLBR of 13–21% for three ovarian stimulation IVF cycles (Ke et al., 2013). In the present study, higher LBR per cycle (18.3%) and CLBR (31.9%) were observed compared with 2.6–6.3% of LBR per cycle and 7.4–9.9% of LBR per woman in prior investigations (Busnelli et al., 2015; La Marca et al., 2015; Polyzos et al., 2012, 2014). One of the possible explanations is the different age composition in patients enrolled. Fewer women exceeding 40 years (36.9%) were included in the present study, whereas nearly 50% and 80% women of advanced age were included in the aforementioned studies (Busnelli et al., 2015; La Marca et al., 2015; Polyzos et al., 2014). For women of advanced age a similar low LBR (9.0%) was found in the present study. The latter findings are consistent with previous reports with LBR varying from 4.5% up to 9.7% of LBR (Klipstein et al., 2005; Ron-El et al., 2000; Tsafrir et al., 2007). Another explanation might be that in our study more oocytes were retrieved compared with other studies (Busnelli et al., 2015; La Marca et al., 2015; Polyzos et al., 2014). More obtained oocytes may result in better pregnancy results (Baka et al., 2006; Polyzos et al., 2014; Sunkara et al., 2011; Timeva et al., 2006; Ulug et al., 2003).

It has been reported that 90% of pregnancies were achieved in the first three cycles of IVF–embryo transfer (Vrtacnik et al., 2014; Witsenburg et al., 2005). Stern et al. reviewed 27,906 cycles of IVF/ICSI–embryo transfer and demonstrated increasing CLBR during the first four cycles. During the subsequent cycles, no significant increase in pregnancies rate was achieved (Stern et al., 2010). Similarly, most live births were obtained during the first three cycles in this study. The Ethics Committee of the American Society for Reproductive Medicine recommends that clinicians can refuse or stop providing fertility treatment for those whose prognosis is very poor or futile ("futility" being defined as treatment that has a < 1% chance of achieving a live birth; "very poor prognosis" being defined as treatment for which the odds of achieving a live birth range from 1% to 5% per cycle) (Ethics Committee of American Society for Reproductive Medicine, 2012). Given this low rate of live birth (2.4%), a treatment consisting of more than three cycles of IVF in women with POR should not be recommended.

It has been shown that female fertility tends to diminish along with increasing age, finally leading to poor pregnancy results during infertility treatment. Moreover, pregnancies are often accompanied by complications in older women. A

Table 2 Rates of live birth and cumulative live birth during IVF cycles ($n = 700$).

Consecutive cycles	*Cycle 1*	*Cycle 2*	*Cycle 3*	*≥Cycle 4*	*P-value*
Total cycles (*n*)	401	194	63	42	
Live births (*n*)	89	31	7	1	
LBR/cycle (%)	22.2[a,b,c]	16.0[b,c]	11.1	2.4	<0.01
CLBR (*N*)	89	120	127	128	
CLBR/woman (%)	22.2[a,b,c]	29.9[b,c]	31.7	31.9	<0.01

CLBR = cumulative live-birth rate; LBR = live-birth rate.
[a]Significant difference was found compared with cycle 2. (Bonferroni corrected *P*-value of 0.008 [6 tests in total] was set as the threshold.)
[b]Significant difference was found compared with cycle 3. (Bonferroni corrected *P*-value of 0.008 [6 tests in total] was set as the threshold.)
[c]Significant difference was found compared with the group of ≥4 consecutive cycles. (Bonferroni corrected *P*-value of 0.008 [6 tests in total] was set as the threshold.)

Table 3 Live-birth rates and cumulative live-birth rates stratified by age and cycle number.

	<35 years (n = 150)	*35–39 years (n = 103)*	*≥40 years (n = 148)*	*P-value*
Cycle 1				
Cycles (*n*)	150	103	148	
Live births (*n*)	54	20	15	
LBR/cycle (%)	36.0[a,b]	19.4	10.1	<0.01
Cycle 2				
Cycles (*n*)	64	50	80	
Live births (*n*)	16	8	7	
LBR/cycle (%)	25.0[b]	16.0	8.8	0.02
Cycle 3				
Cycles (*n*)	16	16	31	
Live births (*n*)	1	3	3	
LBR/cycle (%)	6.3	18.8	9.7	NS
≥Cycle 4				
Cycles (*n*)	10	13	19	
Live births (*n*)	1	0	0	
LBR/cycle (%)	10.0	0	0	NA
Total				
Cycles (*n*)	240	182	278	
CLBR (*n*)	72	31	25	
LBR/cycle (%)	30.0[a,b]	17.0[b]	9.0	<0.01
CLBR/woman (%)	48.0[a,b]	30.1	16.9	<0.01

CLBR = cumulative live-birth rate; LBR = live-birth rate; NA = not available; NS = not statistically significant.
[a]Significant difference was found compared with the group aged < 35 years. (Bonferroni corrected *P*-value of 0.017 [3 tests in total] was set as the threshold.)
[b]Significant difference was found compared with the group aged ≥ 40years. (Bonferroni corrected *P*-value of 0.017 [3 tests in total] was set as the threshold.)

systematic review, including 19 studies applying different POR definitions, concluded that younger patients had higher pregnancy rates compared with older women (Oudendijk et al., 2012). Similarly, in the present study younger patients also had a reasonable CLBR. However, it should be noted that the advantage of higher LBR for younger patients only existed during the first two cycles and the difference vanished in cycle 3.

As already known, the quantity and quality of oocytes equally contribute to pregnancy results in older women. Nowadays, the markers for ovarian reserve, such as AFC and AMH, are better at predicting the number of oocytes rather than oocyte quality (Broer et al., 2009, 2013; Ferraretti and Gianaroli, 2014). Few predictors for oocyte quality are available except for age (Broer et al., 2013). Hence, stratification according to age in women with POR might be helpful to predict the outcome of assisted reproductive treatment. Our findings suggest that patients with POR or high risk for POR should seek infertility treatment as early as possible.

Treatments for POR patients have long been a tough challenge for reproductive specialists. We calculated LBR and CLBR in a large POR population during consecutive treatment cycles. Our major findings do provide good information for patients

with POR to help with balanced decision-making about their infertility treatment. Meanwhile, the present study defining POR according to the Bologna criteria is capable of providing comparative data for new treatment strategies. Still, some limitations should be held in mind. First, this is a retrospective, single-centre, and observational cohort study, instead of prospective randomized clinical trial. Secondly, other factors impacting on the outcome of assisted reproductive treatment, such as endometrial receptivity and male factor, were not considered when analysing LBR and CLBR.

Younger patients with POR fulfilling the Bologna criteria showed a reasonable LBR during the first three treatment cycles, in contrast to older women with POR. More IVF treatments after three unsuccessful cycles are not indicated to be efficient for patients with POR.

Acknowledgements

The authors thank the participation of all patients. This research was supported by National Basic Research Program of China (973 Program) (2012CB944700), the State Key Program of National Natural Science Foundation of China (81430029), and the National Natural Science Foundation of China (81522018, 81270662, 81471509).

References

Baka, S., Makrakis, E., Tzanakaki, D., Konidaris, S., Hassiakos, D., Moustakarias, T., Creatsas, G., 2006. Poor responders in IVF: cancellation of a first cycle is not predictive of a subsequent failure. Ann. N. Y. Acad. Sci. 1092, 418–425.

Broer, S.L., Mol, B.W., Hendriks, D., Broekmans, F.J., 2009. The role of antimullerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. Fertil. Steril. 91, 705–714.

Broer, S.L., van Disseldorp, J., Broeze, K.A., Dolleman, M., Opmeer, B.C., Bossuyt, P., Eijkemans, M.J., Mol, B.W., Broekmans, F.J., 2013. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach. Hum. Reprod. Update 19, 26–36.

Busnelli, A., Papaleo, E., Del, P.D., La Vecchia, I., Iachini, E., Paffoni, A., Candiani, M., Somigliana, E., 2015. A retrospective evaluation of prognosis and cost-effectiveness of IVF in poor responders according to the Bologna criteria. Hum. Reprod. 30, 315–322.

Ethics Committee of American Society for Reproductive Medicine, 2012. Fertility treatment when the prognosis is very poor or futile: a committee opinion. Fertil. Steril. 98, e6–e9.

Ferraretti, A.P., Gianaroli, L., 2014. The Bologna criteria for the definition of poor ovarian responders: is there a need for revision. Hum. Reprod. 29, 1842–1845.

Ferraretti, A.P., La Marca, A., Fauser, B.C., Tarlatzis, B., Nargund, G., Gianaroli, L., 2011. ESHRE consensus on the definition of "poor response" to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum. Reprod. 26, 1616–1624.

Garcia, J.E., Jones, G.S., Acosta, A.A., Wright, G., Jr., 1983. Human menopausal gonadotropin/human chorionic gonadotropin follicular maturation for oocyte aspiration: phase II, 1981. Fertil. Steril. 39, 174–179.

Kahraman, K., Berker, B., Atabekoglu, C.S., Sonmezer, M., Cetinkaya, E., Aytac, R., Satiroglu, H., 2009. Microdose gonadotropin-releasing hormone agonist flare-up protocol versus multiple dose gonadotropin-releasing hormone antagonist protocol in poor responders undergoing intracytoplasmic sperm injection-embryo transfer cycle. Fertil. Steril. 91, 2437–2444.

Ke, H., Chen, X., Liu, Y.D., Ye, D.S., He, Y.X., Chen, S.L., 2013. Cumulative live birth rate after three ovarian stimulation IVF cycles for poor ovarian responders according to the bologna criteria. J. Huazhong Univ. Sci. Technol. Med. Sci. 33, 418–422.

Klipstein, S., Regan, M., Ryley, D.A., Goldman, M.B., Alper, M.M., Reindollar, R.H., 2005. One last chance for pregnancy: a review of 2,705 in vitro fertilization cycles initiated in women age 40 years and above. Fertil. Steril. 84, 435–445.

La Marca, A., Grisendi, V., Giulini, S., Sighinolfi, G., Tirelli, A., Argento, C., Re, C., Tagliasacchi, D., Marsella, T., Sunkara, S.K., 2015. Live birth rates in the different combinations of the Bologna criteria poor ovarian responders: a validation study. J. Assist. Reprod. Genet. 32, 931–937.

Luke, B., Brown, M.B., Wantman, E., Lederman, A., Gibbons, W., Schattman, G.L., Lobo, R.A., Leach, R.E., Stern, J.E., 2012. Cumulative birth rates with linked assisted reproductive technology cycles. N. Engl. J. Med. 366, 2483–2491.

Malizia, B.A., Hacker, M.R., Penzias, A.S., 2009. Cumulative live-birth rates after in vitro fertilization. N. Engl. J. Med. 360, 236–243.

Oudendijk, J.F., Yarde, F., Eijkemans, M.J., Broekmans, F.J., Broer, S.L., 2012. The poor responder in IVF: is the prognosis always poor?: a systematic review. Hum. Reprod. Update 18, 1–11.

Pandian, Z., McTavish, A.R., Aucott, L., Hamilton, M.P., Bhattacharya, S., 2010. Interventions for "poor responders" to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF). Cochrane Database Syst. Rev. (1), CD004379.

Polyzos, N.P., Devroey, P., 2011. A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel. Fertil. Steril. 96, 1058–1061, e7.

Polyzos, N.P., Blockeel, C., Verpoest, W., De Vos, M., Stoop, D., Vloeberghs, V., Camus, M., Devroey, P., Tournaye, H., 2012. Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria. Hum. Reprod. 27, 3481–3486.

Polyzos, N.P., Nwoye, M., Corona, R., Blockeel, C., Stoop, D., Haentjens, P., Camus, M., Tournaye, H., 2014. Live birth rates in Bologna poor responders treated with ovarian stimulation for IVF/ICSI. Reprod. Biomed. Online 28, 469–474.

Polyzos, N.P., Corona, R., Van De Vijver, A., Blockeel, C., Drakopoulos, P., Vloeberghs, V., De Vos, M., Camus, M., Humaidan, P., Tournaye, H., 2015. Corifollitropin alfa followed by hpHMG in GnRH agonist protocols. Two prospective feasibility studies in poor ovarian responders. Gynecol. Endocrinol. 31, 885–890.

Ron-El, R., Raziel, A., Strassburger, D., Schachter, M., Kasterstein, E., Friedler, S., 2000. Outcome of assisted reproductive technology in women over the age of 41. Fertil. Steril. 74, 471–475.

Stern, J.E., Brown, M.B., Luke, B., Wantman, E., Lederman, A., Missmer, S.A., Hornstein, M.D., 2010. Calculating cumulative live-birth rates from linked cycles of assisted reproductive technology (ART): data from the Massachusetts SART CORS. Fertil. Steril. 94, 1334–1340.

Sunkara, S.K., Rittenberg, V., Raine-Fenning, N., Bhattacharya, S., Zamora, J., Coomarasamy, A., 2011. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum. Reprod. 26, 1768–1774.

Sunkara, S.K., Coomarasamy, A., Faris, R., Braude, P., Khalaf, Y., 2014. Long gonadotropin-releasing hormone agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. Fertil. Steril. 101, 147–153.

Timeva, T., Milachich, T., Antonova, I., Arabaji, T., Shterev, A., Omar, H.A., 2006. Correlation between number of retrieved oocytes and pregnancy rate after in vitro fertilization/intracytoplasmic sperm infection. Scientificworldjournal 6, 686–690.

Tsafrir, A., Simon, A., Revel, A., Reubinoff, B., Lewin, A., Laufer, N., 2007. Retrospective analysis of 1217 IVF cycles in women aged 40 years and older. Reprod. Biomed. Online 14, 348–355.

Ubaldi, F.M., Rienzi, L., Ferrero, S., Baroni, E., Sapienza, F., Cobellis, L., Greco, E., 2005. Management of poor responders in IVF. Reprod. Biomed. Online 10, 235–246.

Ulug, U., Ben-Shlomo, I., Turan, E., Erden, H.F., Akman, M.A., Bahceci, M., 2003. Conception rates following assisted reproduction in poor responder patients: a retrospective study in 300 consecutive cycles. Reprod. Biomed. Online 6, 439–443.

Venetis, C.A., Kolibianakis, E.M., Tarlatzi, T.B., Tarlatzis, B.C., 2010. Evidence-based management of poor ovarian response. Ann. N. Y. Acad. Sci. 1205, 199–206.

Vrtacnik, U., Vrtacnik, B.E., Devjak, R., 2014. Cumulative delivery rate after providing full reimbursement in vitro fertilization programme: a 6-years survey. Biomed Res. Int. 2014, 850478.

Witsenburg, C., Dieben, S., Van der Westerlaken, L., Verburg, H., Naaktgeboren, N., 2005. Cumulative live birth rates in cohorts of patients treated with in vitro fertilization or intracytoplasmic sperm injection. Fertil. Steril. 84, 99–107.

Declaration: The authors report no financial or commercial conflicts of interest.

Received 27 November 2015; refereed 17 February 2016; accepted 24 February 2016.