Received: 17 December 2018 | Accepted: 19 December 2018

DOI: 10.1111/jebm.12346

GUIDELINE

WILEY

A Chinese practice guideline of the assisted reproductive technology strategies for women with advanced age

Li Jiang[1] | **Yaolong Chen**[2,3,4] | **Qi Wang**[5,6] | **Xiaoqin Wang**[2,3,4] | **Xufei Luo**[2,3,4] | **Junqiao Chen**[7] | **Hongjing Han**[1] | **Yingpu Sun**[8] | **Huan Shen**[1] | **Chinese Society of Reproductive Medicine (CSRM)**

[1]Reproductive Medicine Center, Peking University People's Hospital, Beijing, China

[2]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu, China

[3]Chinese GRADE Center, Lanzhou, China

[4]WHO Collaborating Centre for Guideline Implementation and Knowledge Translation, Lanzhou, China

[5]Health Policy PhD Program, Department of Health Research Methods, Evidence and Impact, Faculty of Health Sciences, McMaster University, Hamilton, Canada

[6]McMaster Health Forum, McMaster University, Hamilton, Canada

[7]Faculty of Science, University of Lisbon, Lisbon, Portugal

[8]Reproductive Medicine Center, Zhengzhou University First Affiliated Hospital, Zhengzhou, Henan, China

Correspondence
Huan Shen, Reproductive Medicine Center, Peking University People's Hospital, 11 Xizhimen South Street, Beijing, China.
Email: rmivf@sina.com

Additional Correspondence
Yingpu Sun, Reproductive Medicine Center, Zhengzhou University First Affiliated Hospital, Zhengzhou, Henan, China.
Email: syp2008@vip.sina.com

Li Jiang and Yaolong Chen contributed equally to this study.

Abstract

More women postpone childbearing nowadays while female fertility begins to decline with advancing age. Furthermore, with the rolling out of the two-child policy, there is a huge demand for a second child for Chinese aged women. There are various assisted reproductive technology (ART) strategies applied for age-related infertility without solid evidence. On behalf of the Society of Reproductive Medicine, Chinese Medical Association, we would like to develop a Chinese guideline of ART strategies for age-related infertility. This guideline was produced following the recommendations for standard guidelines described in the 2012 WHO Handbook for guideline development. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was also followed. A protocol was formulated and a Guideline Development Group was formed with specialists of reproductive medicine, methodologists from Chinese GRADE working group, and patient representative. Questions regarding the ART strategies for aged infertility were formulated and 8 most important ones were chosen to be structured in PICO format (Population, Intervention, Comparison, Outcomes). Comprehensive search and review of the literature were performed and the quality of the evidence was assessed and rated based on certain criteria and be categorized as high, moderate, low, or very low. Twenty-five recommendations were formulated among members of the Guidelines Development Group (Delphi method) basing on the overall quality of the evidence, in addition to the balance between benefits and harms, values and preferences, and resource implications. The final recommendations were agreed on by consensus during face-to-face meetings. This is the first Chinese practice guideline in reproductive medicine developed following the standard and scientific method.

KEYWORDS

advanced maternal age, assisted reproductive technology, evidence-based clinical practice guideline, infertility

1 | BACKGROUND AND OBJECTIVES

With the increasing number of women who postpone marriage and childbearing nowadays, the proportion of first birth occurring among women with advanced maternal age (AMA) in developed countries such as the United States, Canada, Australia, and New Zealand was increasing accordingly.[1] China is no exception. In 2007, the proportion of the advanced maternal woman was 8.56%,[4] comparing to 2.96% in 1996. Particularly, since October 2015, China rolled out the two-child policy (one couple is allowed to have the second child) across the country, which further promoted the proportion of births occurred among women with advanced age.[5] However, women's fecundity declines with increasing age.[9] Those with a decreased fecundity always need assisted reproductive technology (ART) to help them with

conception. ART is a series of technologies that allows infertile couples to achieve pregnancy via managing gametes and embryos using micromanipulation techniques, including artificial insemination (AI), in vitro fertilization and embryo transfer (IVF-ET), and derived technologies.[10] Although effectively improving the pregnancy rate and birth rate, particularly for women with advanced age, the academics still fail to reach consensus on many topics and to formulate a normative clinical practice guideline.

In 1958, the International Federation of Gynecology and Obstetrics defined "advanced maternal age" as pregnant women aged 35 years and older. Comparing to their younger counterparts, women with an advanced maternal age are exposed to a higher pregnancy risk, not only a higher risk of various obstetric complications, but also a poorer birth outcome and prognosis for both the mothers and newborns.[6–8] In the area of reproductive medicine, given the positive association between women's age and ART outcomes, the ART strategies for women with advanced age vary from those for younger women. However, the academics have not reached a consensus on the cutoff value for "women with advanced age" and whether to follow the same age as "advanced maternal age."

Several Chinese expert consensus statements have been developed to address the ART strategies for women with advanced age,[11,12] and there have been a couple of relevant recommendations toward ART strategies for women with advanced age from other countries' guidelines or concensus.[13–16] However, there is no guideline specifically aiming at this group of women yet, and several problems exist. Firstly, the clinical questions addressed in international guidelines cannot reflect the focus of the Chinese context, and the recommendations are seldom based on evidence from China. Secondly, the Appraisal of Guidelines for Research and Evaluation (AGREE) scores are low for previous Chinese expert consensus, either due to the lack of supporting evidence or because the evidence is of poor quality. Thirdly, some of the recommendations, both domestic and overseas, are vague and impractical, especially those targeting women with advanced age. Finally, those recommendations hardly took the patients' preference and values into consideration.

To solve the abovementioned problems, we formed a multidisciplinary working group and followed the standard method and process of developing an evidence-based clinical practice guideline to develop this practice guideline of the ART strategies for women with advanced age, aiming at standardizing the application of ART in women with advanced age and providing the appropriate support for health workers/practitioners in reproductive medicine facilities.

2 | METHOD

The guideline was developed following the method process recommended by 2014 WHO Handbook for guideline development,[17] and also referred to AGREEII, "The basic method and procedure of developing or updating the clinical guideline of diagnosis and treatment" published by Chinese Medical Association in 2016 and "The standard of formulating guidelines and consensus" drew up by Chinese Society of Reproductive Medicine in 2016.[18,19] The final guideline was reported according to the Reporting Items for Practice Guidelines in Healthcare (RIGHT, http://www.right-statement.org).[20] The flow chart of the guideline development process is provided in the Appendix.

2.1 | Sponsor and supporters

The Chinese Society of Reproductive Medicine, which affiliated to Chinese Medical Association, initiated and took charge of the development of this guideline, whereas the Chinese GRADE Center/Evidence-Based Medicine Center of Lanzhou University provided the methodological support.

2.2 | Registration and protocol composing

This guideline has been registered on the International Practice Guidelines Registry Platform (International practice guideline registry platform, IPGRP)[21] both in English and Chinese (registration number: IPGRP-2017CN005). The guideline's protocol can be obtained from IPGRP if required.

2.3 | Users and targeting audience

This guideline mainly applies to facilities providing reproductive services to infertility couples. The principal potential users are Chinese clinical professionals (including clinical practitioners, embryologists, and nurses). The primary target audience is Chinese women receiving ART at an advanced age (≥35 years old).

2.4 | Guideline working groups

The five working groups were formed for this guideline, including guideline steering committee, guideline development group, secretariat, evidence evaluation group, and external review group. Experts from areas of reproductive medicine, embryology, obstetrics, gynecology, health economics, evidence-based medicine, etc. participated in the developing process. One patient representative was also included in the formulation of the final recommendations.

2.5 | Conflict of interest statement

All members of the guideline working groups have filled out the Declaration of Interest form and declared no conflict of interest directly related to this guideline.

2.6 | Identify and selection of clinical questions

Two rounds of questionnaire survey were conducted to identify clinical problems of the practitioners' interest. Three hundred thirty-three copies of questionnaire were collected from 105 facilities all over mainland China, covering all the 31 provinces, municipalities, and autonomous regions. After deduplication and combination, 21 most important questions were identified, and the top eight of them were included in this guideline after discussion within the working groups.

TABLE 1 GRADE decision-making tool

Decision-making process	Grading score on recommendations				
	1	2	0	−2	−1
Balance of benefits and harms	The benefits outweigh the harms	The benefits possibly outweigh the harms	Equal benefits and harms or uncertainty about the stability of benefits versus harms	The harms probably outweigh the benefits	The harms outweigh the benefits
Recommendation	Strong recommendation	Weak recommendation	No recommendation for or against the intervention	Weak recommendation	Strong recommendation
Voting result					

TABLE 2 Level and definition of quality of evidence and strength of recommendations

Grade	Definition
Quality of evidence	
High	We are very confident that the actual effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident of the effect estimate: The actual effect is likely to be close to the evaluation of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the evaluation of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Recommended strength	
Strong (1)	Clearly shows the benefits of intervention outweigh the harms or more harms than benefits
Weak (2)	Uncertain about the benefits and harms or the benefits and harms are tantamount regardless of the quality of evidence

2.7 | Evidence search, evaluation, and grading

Based on the included clinical questions, the guideline working group systematically searched the following databases: (a) Systematic review and meta-analysis: PubMed, Epistemonikose, the Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), WanFang Data, and CBM; (b) Clinical trials: Up To Date, DynaMed, CNKI, WanFang Data, CBM, and PubMed; (c) Relevant reproductive medicine guidelines: the National Institute for Health Care and Excellence (NICE), National Guideline Clearinghouse, European Society of Human Reproduction and Embryology (ESHRE), and American Society for Reproductive Medicine (ASRM). Supplementary search in Google Scholar and official websites for specific journals were performed as well. All the databases were searched from inception to April 1, 2017.

The following tools were employed to assess the methodological quality or risk of bias for the included studies: Assessing the Methodological Quality of Systematic Reviews (AMSTAR) scale was used to evaluate the methodological quality for systematic review, meta-analysis, and network meta-analysis[22]; Cochrane risk of bias tool[23], quality assessment of diagnostic accuracy studies,[24] and Newcastle-Ottawa Scale were applied to evaluate the methodological quality for corresponding clinical researches.[25] Two independent reviewers performed the assessment process, and any disagreements were resolved by discussion or consultation for a third member. Grading of Recommendations Assessment, Development and Evaluation (GRADE)[26,27] approach was applied to evaluate the body of evidence and to formulate the recommendations. Please refer to Tables 1 and 2 for GRADE decision-making tool and GRADE quality of evidence and recommendations.

2.8 | Patients' preference and value

The guideline working group conducted a questionnaire survey on some of the included clinical questions in which patients' preferences and value may play a part and received 50 feedbacks. The evidence evaluation group analyzed the results and took them into account when formulating the final recommendations

2.9 | Formulation and update of the recommendations

Based on the evidence, patients' preference and value, the cost of interventions, and balance of advantages and disadvantages, 25 final recommendations were formulated after a one-round Delphi survey and four face-to-face consensus meetings.

The guideline working group will update the guideline following the international guideline updating process, if necessary.

2.10 | Dissemination and application

The guideline has two versions, the Chinese language version is published in the Chinese Journal of Evidence-based Medicine, and the

English language version is the current version. After the approval and publication of this guideline, the guideline will be disseminated via (a) continuing education activities in relevant academic conferences; (b) organizing workshops to facilitate the clinical practitioners, pharmacists comprehensively understand and correctly use the recommendations; (c) publishing summary/review articles in Chinese academic journals; (d) social media and other printed media, for example, Chinese Reproductive Medicine Society's website, Wechat, Weibo.

And we planned to update this guideline in 2021-2023 following the international guideline updating process.[28]

3 | RESULTS

This guideline contains 25 final recommendations under eight areas: health promotion, ovarian reserve evaluation and intervention, selection of ART approach, controlled ovarian hyperstimulation (COH), selection of fertilization method, preimplantation genetic screening (PGS), embryo implantation, luteal phase support, and fetal deduction. All the recommendations are listed in Frame 1.

Frame 1. Summary of the Recommendations

1. **Health promotion (N = 5)**
   - Age is an independent risk factor for women's fecundity and their pregnancy outcomes. Based on the relevant evidence both domestic and overseas, we recommend 35 years old as the cut-off value for advanced maternal age in the area of reproductive medicine. (1A)
   - For women 35 years old and older, the risk of spontaneous miscarriage, various obstetric complications and neonatal congenital disabilities increase significantly with age, while the pregnancy rate and live birth rate decline significantly with age. (1A)
   - We suggest women aged 35 years and elder to receive clinical evaluation (including ovarian reserve function evaluation) and proper treatment for infertility if not pregnant after six months' regular, unprotected sex. (2B)
   - Women aged 35 years and elder who will receive ART should be informed that the cumulative pregnancy rate and live birth rate of IVF decrease with age, during the miscarriage rate increase with age. (1B)
   - We suggest health education for women with advanced age when receiving ART. Psychological counselling or intervention may be provided for certain patients. (2C)
2. **Ovarian reserve evaluation and intervention (N = 5)**
   - Currently, there are no acknowledged diagnostic criteria for diminished ovarian reserve (DOR). We suggest a comprehensive evaluation involving age, basal hormone level, anti-müllerian hormone (AMH) and antral follicle count (AFC), etc. (2C)
   - We suggest a combination of basal follicular stimulating hormone (FSH), estradiol (E_2), AMH etc. for evaluating ovarian reserve. However, such evaluation may not be necessarily associated with women's fertility outcome but mainly predict the ovarian response to COH. (2C) Inhibin B (INH B) should not be used as a marker for DOR. (1B)
   - We suggest antral follicle count (AFC) under ultrasound as a marker in evaluating ovarian reserve function, (2C) and do not suggest ovarian volume (OV) for diagnosing DOR. (1B)
   - For infertile women with DOR, dehydroepiandrosterone (DHEA) may improve the ovarian response, the quality of the oocyte and embryo, the number of retrieved oocytes as well as the clinical pregnancy rate. However, there is insufficient evidence. (2C)
   - Growth hormone (GH) might improve the ovarian response and live birth rate for women with DOR or poor ovarian response, with insufficient evidence. (2C)
3. **Selection of ART approach (N = 1)**
   - Age is significantly associated with the pregnancy rate of IUI. The clinical pregnancy rate of IUI for women ≥30 years old declines with advanced age, while such a decline is more dramatic after age 40. We, therefore, do not recommend women greater than 40 years to receive IUI but to receive IVF instead to increase their chance of pregnancy. (1B)
4. **Controlled ovarian hyperstimulation protocols (N = 2)**
   - For women ≥35 years old and receiving the down-regulation protocol for COH, recombinant LH (rLH) supplementation, particularly in the middle or late follicular phase if LH <2 mIU/ml, is recommended. It may improve pregnancy outcomes such as embryo implantation rate and clinical pregnancy rate. (1C)
   - For women ≥35 years old who receiving the antagonist protocol for COH, there is no evidence regarding the effectiveness of the supplementation of LH/rLH in benefiting the pregnancy outcomes. (2B)
5. **Selection of fertilization (N = 2)**
   - The choice of fertilization (IVF or ICSI) is not made according to women's age. (1B)
   - For infertile women caused by non-male factors, compared to IVF, ICSI could not improve the pregnancy outcomes after fertilization but increase the cost in a similar cycle. We, therefore, recommend IVF for these patients. (1B)

6. **Embryo selection—PGS (N = 3)**
   - For women with advanced age who receive ART, detailed information regarding the advantages and disadvantages of PGS should be provided beforehand to help to make the decision about whether PGS is necessary for them. (2C)
   - For women with advanced age and receiving ART, preimplantation genetic screening (PGS) (e.g. CGH) may improve the embryo implantation rate and ongoing pregnancy rate. But meanwhile, it may be accompanied with a certain risk of misdiagnosis and embryo impairment. (2C)
   - We suggest women greater than 38 years old, or with a history of recurrent implantation failure/recurrent spontaneous abortion consider PGS. (2C)
7. **Embryo transfer (N = 2)**
   - For women aged between 35 and 37 years old and with a good prognosis, we recommend elective single embryo transfer to decrease the multi pregnancy rate and the risk for maternal and fetal complications. (1A)
   - For women >37 years old or with a poor prognosis, we suggest double embryos transfer. But the patients must be informed of the risk of multi pregnancy and maternal and fetal complications. (2B)
8. **Luteal phase support and fetal deduction (N = 5)**
   - There are no statistical differences in live birth rate, clinical pregnancy rate, ongoing pregnancy rate, miscarriage rate and multiple pregnancy rate etc. for various luteal support approaches, i.e.muscular injection of progesterone, vaginal progesterone gel, and oral progesterone. (1B)
   - Intramuscular progesterone injection may result in certain side effects, e.g. local tender spot, swelling, infection, whose incidence elevate with dose. (2C)
   - Patient preference should be considered when making decisions on the approach of LPS. (2C)
   - A fetal deduction is suggested for women with advanced age and a twin pregnancy since it will decrease the risk of preterm birth and low birth weight neonate and increase the term pregnancy rate, the mean pregnancy duration and neonatal birth weight. Patients should be comprehensively informed of the relevant risks if choosing not to have a fetal deduction. (2C)
   - We suggest fetal deduction performed in the first or second trimester. Women with high-risk factors (≥40 years old, or with a history of recurrent miscarriage, or with a family history of hereditary disease, or with the risk of fetal inherently diseases) may wait till the second trimester to receive fetal deduction (2C)

Recommendations 1 and 2

- Age is an independent risk factor for women's fecundity and their pregnancy outcomes. Based on the relevant evidence both domestic and overseas, we recommend 35 years old as the cutoff value for women of advanced age in the area of reproductive medicine. (1A)
- For women 35 years and older, the risk of spontaneous miscarriage, various obstetric complications, and neonatal congenital disabilities increase significantly with age, whereas the pregnancy rate and live birth rate decline considerably with age. (1A)

For women 35 years and older, the risk of spontaneous miscarriage, various pregnancy complications, and neonatal birth defects, as well as the incidence of infertility increase significantly, whereas the pregnancy rate and live birth rate decline significantly with age.[29–33] Advanced age is associated with a decreased fecundity and a higher incidence of female infertility: 6% at age 20-24, 9% at age 25-30, 15% at age 30-35, 30% at age 35-40, and 64% at age 40~45.[34] The main explanation for such declining is that women's ovarian reserve and oocyte quality decreases with age, but the increased prevalence of uterine diseases including leiomyoma, adenomyosis and endometrial lesions also have a role in the decline of fecundity for women with advanced age.[36] The 2012 guideline from the Society of Obstetrics and Gynaecology of Canada (SOGC) pointed out: The probability of achieving pregnancy in one menstrual cycle declines with age, approaching 0% around 46 years old.[9]

Meanwhile, the spontaneous abortion rate is approximately 40% for women 35-45 years old and 60–65% for women aged 45 and older. Therefore, the proportion of live birth to women between the age of 38 and 40 years is 19.2%, which decreases to 12.7%, 5.1%, and 1.5% among women between 39 and 42, 43 and 45, and greater than 45 years old.[35]

Furthermore, the risk of various obstetric complications is associated with age. Women of 45 years old are 2.7 times, 3.8 times, 10 times, and 1.89 times more likely than their younger counterparts to develop chronic hypertension, diabetes, gestational diabetes, and pregnancy-induced hypertension, respectively.[37] Women who were conceiving after 40 years old and greater face a higher risk of stroke and heart diseases in the future.[38] Neonates born to women with advanced age are more likely to suffer from certain birth defects such as Down's syndrome, cerebral palsy, etc.[31,39]

Recommendation 3

- We suggest women aged 35 years and older to receive clinical evaluation (including ovarian reserve function evaluation) and appropriate treatment for infertility if not pregnant after 6 months' regular, unprotected sex. (2B)

We suggest women aged 35 years and older who are not pregnant after six months' regular and unprotected sex to receive a comprehensive clinical evaluation for infertility. Women ≧40 years old should visit the fertility clinic for fertility evaluation and counselling once started preparing for pregnancy.[40–42] The evaluation mainly includes ovarian reserve function evaluation (blood tests and ultrasound examination) and other infertility tests, such as the tubal patency and uterine/endometrial evaluation (via ultrasound).[43] The progressive decrease in the number and quality of oocyte from fetal life to menopause is the cause of the age-related decline in female fertility.[44] During the reproductive years, there is continued atresia for oocytes. The pool of oocytes decreases to half of its original size at the age around 30, which further decreases to one-sixth at age 35.[49,50] Therefore, an ovarian reserve function evaluation is suggested for women ≥35 years old but not pregnant after 6 months' regular, unprotected sex. If necessary, ART could be applied to these women to shorten the time to pregnancy.

Recommendation 4

- Women aged 35 years and older who will receive ART should be informed that the cumulative pregnancy rate and live birth rate of IVF decrease with age, during the miscarriage rate increase with age. (1B)

Women who plan to receive ART should be informed that the IVF success rate declines with the advancing age and the most optimal age for IVF is 23-39 years old. Statistical data show that the live birth rate per IVF cycle is 33.1% for women younger than 35 years, 26.1% for women aged 35-37, 16.9% for age 38-40, 8.3% for age 41-42, 3.2% for age 43-44, and 0.8% for those 44 years and older. Another research demonstrated that, for women ≥35 years old, the live birth rate per IVF cycle and the cumulative pregnancy rate drop 10% with every 1-2 years increase in age, whereas the miscarriage rate increases 10% accordingly.[40] A Chinese study published in 2014 investigated the association between maternal age and embryo implantation rate and clinical pregnancy rate of IVF cycles performed in women ≥35 years old. They found the IVF success rate for women >43 years old was approaching zero, and the embryo implantation rate of those ≥40 years ($n = 37$, 57 cycles) was significantly lower (8.3%) than that of the age 35 to <37 ($n = 63$, 67 cycles) and age 37 to <40 groups ($n = 55$, 60 cycles).[46] We also suggest performing risk evaluation of adverse fetal outcomes to those who get pregnant via ART, to effectively prevent the poor prognosis due to advanced maternal age.[39,45]

Recommendation 5

- We suggest health education for women with advanced age when receiving ART. Psychological counselling or intervention may be provided for individual patients. (2C)

A psychological evaluation should be considered to be applied to women receiving ART and with an advanced age, who are always accompanied by depression and anxiety. A survey carried out in China after the rolling out of the "two-child" policy in 2016[47] ($n = 110$) revealed a significantly higher score and prevalence of depression (47.37 ± 7.36, 23.63%) and anxiety (43.95 ± 6.32, 32.72%) in women receiving ART and with advanced age comparing to their fertile counterparts in the general population. We, therefore, suggest physicians adopt specific psychological intervention strategies to help those infertile women with advanced age,[48] for example, health promotion and regular seminars in fertility clinics introducing reproductive medicine and ART. Such strategy may benefit the collaboration between physicians and patients, enforce patients' confidence toward the treatment, and improve the psychological health status of infertile women with advanced age.

Recommendations 6 and 7

- Currently, there is no acknowledged diagnostic criterion for diminished ovarian reserve (DOR). We suggest a comprehensive evaluation involving age, basal hormone level, anti-müllerian hormone (AMH), antral follicle count (AFC), etc. (2C)
- We suggest a combination of basal follicular stimulating hormone (FSH), estradiol (E_2), AMH, etc. for evaluating ovarian reserve. However, such evaluation may not be necessarily associated with women's fertility outcome but mainly predict the ovarian response to COH. (2C) Inhibin B (INH B) should not be used as a marker for DOR. (1B)

In terms of hormonal indicator and cytokines, we suggest a combination of basal follicular stimulating hormone (FSH), estradiol (E_2), AMH, and FSH/Luteinizing hormone (LH) to reach the diagnosis of diminished ovarian reserve (DOR). Basal FSH refers to the serum FSH level on the second to fourth day of a natural menstrual cycle.[49] One Chinese clinical randomized research ($n = 284$) showed that FSH was of relatively low sensitivity and specificity in predicting ovarian reserve.[50] But it is still widely used in clinical settings given its low cost and simple test method. Generally, patients with a bFSH ≤ 10 IU/L is considered as with a relatively healthy ovarian reserve, while 10 < FSH ≤ 15 IU/L as borderline, and 15 < FSH ≤ 25 IU/L as with DOR.[51] To be noticed, the value of FSH is related to the assay method and reference standard. Most of the studies take FSH 10IU/L as the cutoff value for predicting DOR,[52–54] whereas some adapt FSH ≥12 or 15 IU/L.[55,56] Although the sensitivity and specificity of FSH in predicting ovarian reserve is low, FSH/LH has a better performance in diagnosing DOR. There is still no consensus regarding its cutoff value, mainly between 2.0 and 3.6. It is commonly considered that an FSH/LH > 3.6 is associated with an inadequate ovarian response to stimulation and a higher cancellation rate.[57]

Basal estradiol (E_2) refers to the serum estradiol level at the second to fourth day of the menstrual cycle. An elevated basal E_2 is thought to emerge earlier than the bFSH elevation and may imply a decreased ovarian reserve. Nonrandomized clinical research ($n = 225$) considered E_2 < 80 mg/dL indicating a healthy ovarian reserve, while the cancellation rate is higher for those with E_2 > 80 mg/dL and their pregnancy rate is lower. A high level of E_2 will inhibit the pituitary producing FSH and may cover up the phenomenon of DOR in

perimenopausal women. Testing both FSH and E_2 may help avoid such influence.

AMH is a cytokine secreted by preantral and small antral follicles, discovered inhibiting the growth of primordial oocyte. It is considered as the most accurate marker reflecting the number of primordial oocytes as well as the most reliable marker indicating the ovarian reserve function.[58,59] A 2015 systematic review[60] (AMSTAR = 9, $n = 5373$) demonstrated the predictive ability of AMH for pregnancy was the greatest in women with DOR, with a sensitivity of 69.9% (95% CI, 61.0-77.9%), a specificity of 64.7% (95% CI, 60.9-68.3%), and an AUC of 0.696 (95% CI, 0.641-0.751). A randomized clinical trial from China ($n = 205$)[61] sorted the markers from high to low regarding their prognostic values of ovarian reserve function as AMH, AFC, bFSH, maternal age, and bFSH/bLH ($P < .05$). It is generally considered that[62] AMH < 0.5 ng/mL indicated an low ovarian reserve of fewer than three follicles in IVF cycles, AMH < 1.0 ng/mL indicated a low ovarian reserve and an inadequate ovarian response, and 1.0 < AMH < 3.5 ng/mL indicated an excellent ovarian response to gonadotropins. When AMH > 3.5 ng/mL, the stimulation should be performed with cautious to avoid ovarian hyperstimulation syndrome (OHSS) since the patients may present an excessive response to gonadotropins. The testing of AMH can be performed on any day of a menstrual cycle given that there is little fluctuation of the AMH level. There is no evidence regarding how frequent the AMH should be reexamined.

But what calls for special attention is that, according to a recent study published in JAMA, biomarkers like AMH and FSH may not be able to assess women's natural fertility, neither predict their chance of pregnancy.[51]

The reliability of Inhibin B (INH B) is low in predicting ovarian reserve, and the majority of studies demonstrated that INH B could not predict pregnancy outcomes.[63–67] Therefore, the 2015 guideline from Amerian Society of Reproductive Medicine (ASRM)[51,68] did not recommend INH B as the predictor of DOR.

Recommendation 8

- We suggest antral follicle count (AFC) under ultrasound as a marker in evaluating ovarian reserve function (2C) and do not indicate ovarian volume (OV) for diagnosing DOR. (1B)

AFC is defined as the number of follicles with 2-10 mm diameter in the ovaries at the start of the menstrual cycle (days 2-4). It is one of the most valuable markers for predicting ovarian reserve function; however, the cutoff level is still controversial, ranging from 5 to 10. Mean ovarian diameter (MOD) is the mean of two perpendicular diameters on the largest cross-sectional sagittal view of any of the ovary. Note that 20 mm is adopted as the cutoff value, and patients with an MOD <20 mm have a poorer IVF outcome.[69] OV was once recommended as the marker for evaluating ovarian reserve function. However, given to its variability in measurement, OV is mainly associated with the number of retrieved oocytes but not with the possibility of pregnancy. It was reported that the accuracy of OV in predicting DOR ranges between 17% and 53%.[64,70] Therefore, 2015 ASRM guideline[51,68] did not recommend OV as a marker for diagnosing DOR.

Whether it is necessary to perform other tests, for example, clomiphene stimulation test (CCCT), gonadotropin-releasing hormone agonist (GnRH-a) stimulation test, etc., depends on the specific situation. These are absolute reliability of these prediction tests; however, they are no longer widely used in clinical settings anymore. Furthermore, the influence of radiotherapy, chemotherapy, and surgery on the ovarian should be taken into account when evaluating the ovarian reserve function.

So far, there is still no consensus in terms of the threshold of each predictor for DOR. Physicians should combine various markers and tests according to a patient's situation to achieve a better evaluation of ovarian reserve.

Recommendation 9

- For infertile women with DOR, dehydroepiandrosterone (DHEA) may improve ovarian response, quality of the oocyte and embryo, number of retrieved oocytes, as well as the clinical pregnancy rate. However, there is insufficient evidence. (2C)

A 2017 systematic review (AMSTAR score = 9, $N = 1208$) showed DHEA might lead to a slightly higher pregnancy rate in patients with DOR (OR = 1.47; 95% CI, 1.09-1.99), but have no significant influence on the number of retrieved oocytes, cycle cancellation rate and the miscarriage rate.[71–73] A systematic review published by Ji et al. (AMSTAR score = 9, $N = 1072$) demonstrated a higher clinical pregnancy rate (OR = 1.64; 95% CI, 1.20-2.24; $P < .001$), an increased number of retrieved oocytes (MD = 1.27; 95% CI, 0.60-1.94; $P = .0002$) and a decreased cycle cancellation rate (OR = 0.54; 95% CI, 0.33-0.87; $P = 0.01$) for IVF/intracytoplasmic sperm injection (ICSI) patients with DOR who use DHEA, but a nonsignificant difference regarding the E2 level on hCG day, total gonadotropin usage, miscarriage rate, etc. The results of Li's systematic review (AMSTAR score = 6, $N = 647$) also indicated that DHEA may improve the clinical pregnancy rate (RR = 2.82; 95% CI, 1.68-4.74; $P < .001$) of IVF/ICSI patients with DOR, but makes no significant difference in the number of retrieved oocytes, embryo implantation rate, and the miscarriage rate etc. However, Dong's study (AMSTAR score = 8, $N = 532$) had a different finding.[74] It revealed that a pretreatment of DHEA for IVF patients with DOR could not improve the clinical pregnancy rate but led to an increased number of retrieved oocytes (MD = 1.27; 95% CI, 0.26-2.29; $P = .03$) and a decreased gonadotropin usage (MD = −528.58; 95% CI, −992.59 to −64.56; $P = .03$), The common side effects of DHEA are acne, obesity, and hirsutism.[75] No severe side effects have been reported yet. But further studies are necessary to investigate its long-term safety. The significant potential risk is developing malignant tumors reliable on estrogen or androgen given that DHEA is the androgen precursor.[76] In conclusion, the evidence of the application of DHEA in DOR patients is still controversial. It is also noteworthy that the included four systematic reviews were all conducted by Chinese research teams. Three of them declared no conflict of interest but did not clarify the funding resources. All four studies did not perform age stratification for women above 35 years old.

Recommendation 10

- Growth hormone (GH) might improve the ovarian response and live birth rate for women with DOR or poor ovarian response, with insufficient evidence. (2C)

A 2017 systematic review (AMSTAR score = 8, $N = 663$) showed GH could significantly increase the clinical pregnancy rate (RR = 1.65; 95% CI, 1.23–2.22; $P < .001$), live birth rate (RR = 1.73; 95% CI, 1.25-2.40; $P < .001$), E2 level on hCG day (SMD = 1.03; 95% CI, 0.18-1.89; $P = .02$), the number of oocyte retrieved (SMD = 1.09; 95% CI, 0.54-1.64; $P < .001$), and MII oocytes (SMD = 1.48; 95% CI, 0.84-2.13; $P < .001$), but decrease the cycle cancellation rate (RR = 0.65; 95% CI, 0.45-0.94; $P = .02$) and the gonadotropin usage (SMD = −0.83; 95% CI, −1.47 to −0.19; $P = .01$), and had no significant effect on embryo implantation rate and fertilization rate. Regarding GH's safety, only one study reported two cases with mild oedema during treatment, whereas the other four studies reported no side effects of GH.[77] A 2009 Cochrane systematic review (AMSTAR score = 10, $N = 401$) demonstrated no difference in IVF outcome measures (live bith rate, clinical pregnancy rate, multipregnancy rate, miscarriage rate, gonadotropin usage, the number of oocytes and embryos, etc.) and adverse events in the routine use of growth hormone adjuvant therapy (growth hormone or growth hormone releasing factor (GRF)) in IVF in women considered as poor responders but a significant difference in both live birth rates (OR = 4.37; 95% CI, 1.06-18.01) and pregnancy rates, favoring the use of growth hormone adjuvant therapy, without increasing adverse events. Only one study reported local reactions at the injection site, but there is no biostatistics difference between GH adjuvant therapy and the placebo group. One study reported severe adverse events (two in the GRF group, moderate salpingitis, and severe OHSS, respectively; four in the placebo group, salpingitis, uterine bleeding, intraperitoneal hemorrhage, and accidental injury, respectively), and there was no significant difference between the two groups.[78]

To sum up, the evidence regarding the effect of GH on clinical pregnancy rate, E2 on hCG day, the number of oocytes retrieved and the dosage of gonadotropin is still inconsistent. For aged women with the poor ovarian response, an RCT conducted in China[79] ($n = 80$, age ≥35) indicated GH combined with gonadotropin could significantly improve the endometrium thickness and the clinical pregnancy rate compared with the gonadotropin only group, but had no significant impact on the cycle cancellation rate and ovulation rate. However, another systematic review demonstrated a higher ongoing pregnancy rate in the GH supplement group in patients with poor ovarian response.[80] Therefore, there is still controversial about the evidence of supplementing GH.

The guideline working group surveyed 50 patients and received 39 feedback questionnaires on this topic. 28% of patients chose to have the pretreatment of GH, 10% chose not, while 62% would like the physicians to make the decision.

Recommendation 11

- Age is significantly associated with the pregnancy rate of IUI. The clinical pregnancy rate of IUI for women ≥30 years old declines with advanced age, while such a reduction is more dramatic after period 40. We, therefore, do not recommend women greater than 40 years to receive IUI but to undergo IVF instead to increase their chance of pregnancy. (1B)

A Chinese study in 2011[81] (943 couples, 1382 cycles) demonstrated the IUI clinical pregnancy rates for age 26-30, 31-35, 36-39, and ≥40 groups are 12.68%, 12.19%, 9.90%, and 3.85%, respectively, with the clinical pregnancy rate significantly lower in the age ≥40 group ($P < .05$). The possible explanation is an increased prevalence of oocyte apoptosis and chromosomal abnormality with age, as well as a decreased number of oocyte mitochondria and cytoplasm ATP concentration.[82] Other mechanisms may include: the hardened zona pellucida of aged oocytes may hamper the penetration of sperms and the hatching of embryos,[83] and the endometrial receptivity decreases with age.[82] Another Chinese retrospective study (153 couples, 250 IUI cycles) found that paternal age had negative impact on IUI outcomes—the pregnancy rate decreased with the increasing paternal age, and the miscarriage rate increased with paternal age ($P < 0.05$). The result of another RCT included infertile patients aged 38-42 years was published in 2014 and showed that the clinical pregnancy rates after two treatment cycles are 21.6%, 17.3%, and 49% for clomiphene citrate (CC)/IUI,[84] gonadotropin/IUI, and IVF groups, respectively, whereas the live birth rates are 15.7%, 13.5%, and 31.4%. These results imply that IVF leads to a significantly higher clinical pregnancy rate and live birth rate than IUI for women ≥40 years old; hence, IVF is a more appropriate strategy for these women.

Recommendation 12

- For women ≥35 years old and receiving the downregulation protocol for COH, recombinant LH (rLH) supplementation, particularly in the middle or late follicular phase if LH <2 mIU/mL, is recommended. It may improve pregnancy outcomes such as embryo implantation rate and clinical pregnancy rate. (1C)

A 2012 systematic review (AMSTAR score = 8, $n = 902$)[85] demonstrated a higher embryo implantation rate (OR = 1.36; 95% CI 1.05-1.78; $P = .32$) and clinical pregnancy rate (OR = 1.37; 95% CI, 1.03-1.83; $P = .20$) when r-LH was supplemented to women ≥35 years old and using the GnRH agonist downregulation protocol for COH. A 2016 RCT ($n = 180$)[86] showed that for IVF/ICSI women <40 years old and with a normal ovarian reserve function, a supplementation of rLH in the GnRH agonist downregulation protocol led to a significantly improvement in E_2 on hCG day, the number of oocytes ≥14 mm, oocytes retrieved and high-quality embryos, the embryo implantation rate, and the clinical pregnancy rate. In 2016, Yang et al conducted a retrospective cohort study ($n = 120$)[87] and found: for women with advanced age and receiving the GnRH agonist down regulation protocol, compared with not adding r-LH, r-LH supplementation on the day that the leading follicle achieves a diameter of 14 mm led to a higher pregnancy rate for women with LH < 1mIU/mL (48.95% vs 35.15%, $P < .05$) and those with LH between 1 and 2mIU/mL (53.13% vs 39.11%, $P < .05$). Furthermore, the miscarriage rate is also lower for women with an LH < 1mIU/mL

(15.78% vs 28.50%, $P < .05$) than that of the control group, but no significant difference was found for women with LH > 2mIU/mL.

Recommendation 13

- For women ≥35 years old and receive the antagonist protocol for COH, there is no evidence regarding the effectiveness of the supplementation of LH/rLH in benefiting the pregnancy outcomes. (2B)

The results of an RCT in 2015 ($n = 240$)[88] demonstrated that, for women ≥35 years old and using GnRH antagonist protocol for COH, there is no significant difference regarding the live birth rate (16.7% vs 17.5%; 95% CI, −9.5-11.2; $P = .864$), embryo implantation rate, as well as the number of oocytes retrieved, embryos and high-quality embryos. The Cochrane systematic review published in 2010 (AMSTAR score = 11, $n = 2612$)[89] also showed no significant difference in clinical pregnancy rate (OR = 0.79; 95% CI, 0.26-2.43; $P = .68$), ongoing pregnancy rate (OR = 0.83; 95% CI, 0.39-1.80; $P = .64$), OHSS incidence rate (OR = 0.68; 95% CI, 0.12-3.99; $P = 0.67$), the amount of rFSH used (WMD = 116.08; 95% CI, −64.30-296.46; $P = .21$), the mean number of oocyte retrieved (WMD = 0.50, 95% CI, −0.68-1.68; $P = .41$) or the miscarriage rate (OR = 2.37; 95% CI, 0.77, 7.33; $P = .13$) when adding rLH to patients receiving GnRH antagonist protocol.

Recommendations 14 and 15

- The choice of fertilization (IVF or ICSI) is not made according to women's age. (1B)
- For infertile women caused by nonmale factors, compared to IVF, ICSI could not improve the pregnancy outcomes after fertilization but increase the cost in a similar cycle. We, therefore, recommend IVF for these patients. (1B)

To choose IVF or ICSI as the approach of fertilization is not based on women's age. Currently, there is no evidence regarding the association of the choice of fertilization and age.

For nonmale factor infertility, the embryo implantation rate, live birth rate, and multi pregnancy rate of IVF cycles are higher than the ICSI cycles, whereas there is no significant difference in their clinical pregnancy rate and the risk of neonatal congenital malformation. We, therefore, suggest IVF for these women. A large retrospective study published in JAMA in 2015 showed a lower embryo implantation rate (23.0% vs 25.2%), live birth rate (36.5% vs 39.2%), and multi pregnancy rate (30.1% vs 31.0%) in ICSI group of women with nonmale factor infertility, compared to the IVF group. They concluded that compared to conventional IVF, ICSI could not improve the ART outcomes.[91] A systematic review in 2003 (AMSTAR = 11, $n = 415$) showed no difference in clinical pregnancy rate between the IVF and ICSI group for women younger than 37 years old (OR = 1.44; 95% CI, 0.95-2.21).[92] In terms of the safety of these two approaches, a 2012 systematic review conducted by Wen Juan et al (AMSTAR score = 6, $n = 156758$) showed both IVF and ICSI would increase the risk of congenital malformation comparing with spontaneous conception (RR = 1.36; 95% CI, 1.25-1.47), but there is no difference between the two groups (RR = 1.05; 95% CI, 0.91-1.20).[93] ICSI has a higher fertilization rate but a lower pregnancy rate. Hence, for nonmale factor infertility, we suggest IVF as the method of insemination.

Recommendation 16

- For women with advanced age who receive ART, detailed information regarding the advantages and disadvantages of PGS should be provided beforehand to help make the decision about whether PGS is necessary for them. (2C)

The 2000 Safety Statement of International Society of Ultrasound in Obstetrics and Gynecology[94] pointed out a comprehensive counselling addressing the pros and cons of whether PGS should be provided to women who are interested in this technique. The 2010 ESHRE guideline[95] identified advanced maternal age (36 years and above, depending on the requirement of individual center) as one of the indications of PGS and recommended a three-step decision-making process provided by the gynecologists in cooperation with the embryologist and the geneticist after consultation with the patients. Whether and when to perform PGS, as well as which oocytes or embryos should be selected for culture and transfer, should be comprehensively discussed among the physicians, embryologists, and the patients. The 2014 guideline of Canada Society of Obstetric and Gynecology[96] came up with the following recommendations: PGS applied to fertile couples must balance the benefit (improve pregnancy outcomes) and potential harms (medical risk and economic burden of IVF); there is still controversy in terms of the improvement of pregnancy outcomes after PGS targeting aneuploidy, and insufficient information about the long-term effect of PGS, which should be explained to patients with the intent to receive PGS. The drawbacks for women with advanced age receiving PGS include a high risk of no embryo for a transfer, given these women are often with DOR and may not be able to obtain many embryos, other medical risks, and the economic burden accompanying IVF and PGS.

Recommendation 17

- For women with advanced age and receiving ART, preimplantation genetic screening (PGS) (eg, CGH) may improve the embryo implantation rate and ongoing pregnancy rate. But meanwhile, it may be accompanied with a particular risk of misdiagnosis and embryo impairment. (2C)

For women with advanced age and receiving ART, preimplantation genetic screening (PGS) (eg, complete 24-chromosome analysis) may improve the embryo implantation rate and ongoing pregnancy rate, but PGS based on fluorescence in situ hybridization (FISH) may worsen the clinical pregnancy rate and live birth rate. Before 2011, FISH is the principal method for PGS. But two crucial prospective randomized controlled trials aiming at women with advanced age showed FISH-PGS group had a significantly lower number of embryos for transfer, ongoing pregnancy, and live birth rate. In 2011, a systematic review and meta-analysis (9RCTs, AMSTAR score = 8, $n = 1589$)[97] also found out that PGS via FISH significantly lowered live birth rate after IVF

for women with advanced maternal age (RD = −0.08, 95% CI, −0.13 to −0.03]) as well as for women with a history of RIF (RD = −0.18, 95% CI, −0.33 to −0.03]). Hence, FISH is no longer applied to PGS. In recent years, the emerging of novel techniques has shed some light on the area of PGS. A systematic review in 2015[98] compared the pregnancy outcomes of the PGS group (using comprehensive chromosome screening, CCS) and the traditional morphology group and demonstrated that CCS-PGS improved the embryo implantation rate, but had no effect on the live birth rate and miscarriage. When combined the results from the included RCT, the results showed that there was no statistical difference in clinical pregnancy rate and ongoing pregnancy rate between the two groups. But the combined results from the included cohort studies indicated CCS-PGS group had a higher clinical and ongoing pregnancy rate.

Regarding the other techniques applied in PGS, a 2015 RCT[99] ($n = 172$) showed next-generation sequencing (NGS) detected all types of aneuploidies of human blastocysts accurately and provided a 100% 24-chromosome diagnosis consistency with the highly validated aCGH method (sensitivity 100%, 95 % CI, 95.32-100%, specificity 100%, 95 % CI, 98.16-100%, positivity prognosis value 100%, negative prognosis value 100%). Moreover, NGS screening identified euploid blastocysts for transfer and resulted in similarly high ongoing pregnancy rates for PGS patients compared to aCGH testing. A 2017 retrospective study[100] revealed that aCGH platform could not identify embryos with chromosomal mosaicism (20-50% aneuploidy) and segmental aneuploidy (≥10 Mbp) precisely, but NGS platform could achieve that.

Nevertheless, the safety of PGS remains a problem that cannot be ignored. PGD/PGS includes the process of embryo biopsy and genetic testing, whereas the main biopsy methods are mechanical, chemical, and laser procedures. Laser technology for breaking the zona pellucida is now the most widely applied method for its convenience and accuracy, but there are still concerns about its thermal effect and its association with a potential embryo impairment.

Recommendation 18

- We suggest women above 38 years old, or with a history of recurrent implantation failure/ recurrent spontaneous abortion consider PGS. (2C)

The Chinese Society of Reproductive Medicine published an expert consensus and specification for next generation sequencing-based PGD/PGS[101] in 2017 and suggested the indication for NGS PGS: women with ≥3 spontaneous miscarriage, or two spontaneous miscarriage, at least one of which is confirmed to be due to chromosomal/genetic abnormalities; women with RIF, which is defined as implantation failure after at least three embryo transfer with good-quality embryos, or after transferring no less than 10 fair embryos; women >38 years old and need ART. The 2010 ESCHRE PGD consortium[95] reported the following indications for PGS: >2 recurrent miscarriages, RIF (≥3 embryo transfers with high-quality embryos or the transfer of ≥10 embryos in multiple transfers), and AMA (>36 completed years). The 2015 Chinese Technique and Standard of PGS/PGD[102] suggested to perform PGS to women with unexplained RIF, RSA, AMA, etc. Another Chinese expert consensus in 2016[103] mentioned that PGS is now for infertile couples with AMA, RIF, RSA, or male-factor infertility. From the above, this guideline suggests women >38 years old, or with a history of RIF, RSA receives PGS.

The guideline working group surveyed 50 patients and received 31 feedbacks on this topic. Note that 58% of the patients chose to follow the physician's suggestion, whereas 29% would like to receive PGS and 13% decided not to.

Recommendation 19

- For women aged between 35 and 37 years old and with a good prognosis, we recommend elective single embryo transfer to decrease the multi-pregnancy rate and the risk for maternal and fetal complications. (1A)

The results from a 2013 Cochrane systematic review (AMSTAR score = 11, $n = 2165$)[104] demonstrated a lower live birth rate (OR = 0.48; 95% CI, 0.39-0.60) and multi-pregnancy rate (OR = 0.12; 95% CI, 0.07-0.20) of elective single embryo transfer for women between 35 and 37 years old and with a good prognosis (with sufficient high-quality embryos) compared to double embryos transfer. A systematic review[105] published in 2010 (AMSTAR score = 11, $N = 1367$) also found the overall live birth rate in a fresh IVF cycle was lower after single than double embryo transfer (OR = 0.50; 95% CI, 0.40-0.63), as was the multiple birth rate (OR = 0.04; 95% CI, 0.01-0.12), for women with a good prognosis. The odds of a term singleton birth (ie, over 37 weeks) after elective single embryo transfer was almost five times higher than the odds after double embryo transfer (OR = 4.93; 95% CI, 2.98-8.18). A retrospective study published in 2014 ($n = 82508$ ART cycles) demonstrated that, among patients younger than 35 years with a favorable prognosis, chances of an excellent perinatal outcome were higher with transferring a single (compared with double) embryos (live birth rate: day 5 embryo, 43% vs 27%; day 3 embryo, 36% vs 30%). Likewise, a higher chance of an excellent perinatal outcome was observed with transferring a single embryo in patients 35-37 years old with a favorable prognosis or patients younger than 35 with an average prognosis.[106] We, therefore, conclude that women with a good prognosis are recommended to receive elective single embryo transfer (based on morphology or PGS) to decrease the risk of multi-pregnancy and complications such as low birth weight, preterm birth, etc. The number of embryos recommended to be transferred in one IVF cycle has been approved by American Society of Reproductive Medicine (ASRM) in 2017[107] (Table 3 and by NICE in 2016[108]; Table 4).

Recommendation 20

- For women >37 years old or with a poor prognosis, we suggest double embryos transfer. But the patients must be informed of the risk of multi-pregnancy and maternal and fetal complications. (2B)

A retrospective cohort study published in 2014 ($n = 82508$ ART cycles) included women aged 35-37 years old and with a poor prognosis (no live birth or extra frozen embryos in previous IVF cycles) or

TABLE 3 Recommendations for the limit to the number of embryos to transfer from 2017 ASRM guideline

	Age (y)			
Prognosis	**<35**	**35-37**	**38-40**	**41-42**
Cleavage-stage embryos				
Euploid	1	1	1	1
Other favorable	1	1	≤3	≤4
All others	≤2	≤3	≤4	≤5
Blastocysts				
Euploid	1	1	1	1
Other favorable	1	1	≤2	≤3
All others	≤2	≤2	≤3	≤3

Note. Justification for transferring additional embryos beyond recommended limits should be clearly documented in the patient's medical record. See text for more complete explanations.
Other favorable 1⁄4 Any ONE of these criteria: Fresh cycle: expectation of one or more high-quality embryos available for cryopreservation, or previous live birth after an IVF cycle; FET cycle: availability of vitrified day 5 or day 6 blastocysts, euploid embryos, 1st FET cycle, or previous live birth after an IVF cycle.
ASRM. Limits on the number of embryos to transfer. Fertil Steril 2017.

women around 40 years old and showed better perinatal outcomes in the double cleavage embryos transfer group compared to the single embryo transfer group.[106] A 2012 prospective cohort study in Lancet (n = 124148 IVF cycles, 33 514 live births; 43.4% of the participants aged 18-34 years old, 25.9% aged 35-37, 15.2% aged 38-39, 12.2% aged 40-42, 2.6% aged 43-44, 0.8% aged 45 years and older) showed that, although triple embryos transfer led to a higher live birth rate (<40 years old; OR = 2.34; 95% CI, 2.09-2.63; ≥40 years old; OR = 3.61; 95% CI, 2.97-4.39) than single embryo transfer, it was also accompanied with a higher risk for preterm birth (<40 years old; OR = 2.27; 95% CI,1.72-2.99) ; ≥40 years old, no significant difference), preterm birth before 33 gestational weeks (<40 years old; OR = 2.70; 95% CI, 1.63-4.48; no significant difference when ≧40 years old), low birth weight newborn (<40 years old; OR = 3.13; 95% CI, 2.41-4.06; ≥40 years old; OR = 1.72; 95% CI, 1.06-3.44). As for the maximum number of embryos in an embryo transfer, the 2017 ASRM guideline and 2016 NICE guideline have made their recommendations.[107,108] If women are complicated with uterine abnormalities, other guidelines should be referred to regarding the number of embryos be transferred.

Cost-effectiveness: A 2007 systematic review (AMSTAR score = 5, N = 1443) concluded that DET is the most expensive strategy, but also the most effective if performed in one fresh embryo transfer cycle. eSET is only preferred from a cost-effective point of view when performed in suitable prognosis patients and when frozen-thawed cycles are included. The results of a modeling study from 2011 showed eSET is likely to be the preferred option for most women aged ≤36 years. The cost-effectiveness of DET improves with age and may be considered cost-effective in some groups of older women. The decision may best be considered on a case-by-case basis for women of 37-39 years old. In 2006, some researchers published a cost-effectiveness analysis and demonstrated the SET strategy is superior to the DET strategy when the number of deliveries with at least one live-born child, incremental cost-effectiveness ratio, and maternal and pediatric complications are taken into consideration. Thus, we conclude that SET is more cost-effective for women with a good prognosis.

Patients' preference and value: One RCT pointed out there may be unavoidable self-selection bias in the research since only a small percentage of candidates volunteer to receive eSET due to the perception by patients that SET could result in lower pregnancy rates and the twin pregnancies are a desirable outcome. If told the risk of twins or multiple pregnancies, most patients would choose to maximize the chance of safe singleton pregnancy and delivery. However, a fetal deduction for multiple pregnancies is not an acceptable option for many women. The 2010 guideline of SOGC suggested that patients should be informed of the risk of twin pregnancy and the fact that the cumulative live birth rate after eSET and DET are similar, which may help increase patients' acceptance of SET.

Recommendation 21

- There is no statistical difference in live birth rate, clinical pregnancy rate, ongoing pregnancy rate, miscarriage rate, multiple pregnancy rate, etc. for various luteal support approaches, that is, muscular injection of progesterone, vaginal progesterone gel, and oral progesterone. (1B)

A systematic review published 2015 (AMSTAR score = 7, n = 2528)[110] found no significant difference in clinical pregnancy rate (OR = 0.93; 95% CI, 0.79-1.09; P = .35), miscarriage rate (OR = 0.75; 95% CI, 0.52-1.08; P = .12), and ongoing pregnancy rate (OR = 0.88; 95% CI, 0.64-1.21; P = .43) between the intramuscular progesterone injection and the vaginal controlled-releasing gel group for IVF patients aged 24-44 years old. In 2016, Zargar et al performed an RCT (n = 612)[111] in women below 40 years old with an infertility duration

TABLE 4 The number of fresh or frozen embryos to transfer in IVF treatment from the NICE guideline

Age (y)	Cycle	Number of embryos to transfer
<37	The first full IVF cycle	Single embryo transfer.
	The second full IVF cycle	Single embryo transfer if one or more top-quality embryos are available. Consider using two embryos if no top-quality embryos are available.
37-39	The first and second full IVF cycles	Use single embryo transfer if there are one or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos.
	The third full IVF cycle	No more than two embryos.
40-42		No more than two embryos.

<5 years and normal menstrual cycle, hormone level, and transvaginal ultrasound manifestation, in which it has been found that the pregnancy rate (25% vs 26.5% vs 26.5%, $P = .3$) and miscarriage rate (5.6% vs 3.8% vs 3.8%, $P = .6$) are not statistically different among the oral, vaginal progesterone, and intramuscular progesterone injection group. Another RCT by Saharkhiz et al in 2016 ($n = 210$)[112] compared the biochemical pregnancy rate (4.0% vs 1.0%), clinical pregnancy rate (31% vs 33%), ongoing pregnancy rate (30% vs 30%), embryo implantation rate (22.0% vs 24.0%), multi pregnancy rate (5.3% vs 7.2%), miscarriage rate (5.0% vs 3.0%), the incidence of adverse effects (92% vs 93%) , and patients' satisfaction and tolerance between oral (20 mg, twice per day) and vaginal micronized progesterone (400 mg, twice per day) group in infertile women aged 20-40 years old and found no significant differences.

Recommendations 22 and 23

- Intramuscular progesterone injection may result in specific side effects, for example, local tender spot, swelling, infection, whose incidence elevate with dose. (2C)
- Patient preference should be considered when making a decision on the approach of LPS. (2C)

In terms of the side effects, since progesterone preparation for intramuscular injection is oil-soluble, it is absorbed slowly at the injection spot and therefore may lead to the formation of local indurations or sterile cysts, which may further cause infection. If injected repeatedly, it may result in local malabsorption and accumulation, with the manifestation of swelling, tender spot accompanied by itching and pain.[113] An RCT conducted by Zhang et al in 2012 ($n = 150$)[114] showed a dose-dependent association of intramuscular progesterone injection and the incidence of adverse effects—the rate of adverse effects in the 20 mg/mL group is higher than that of the 10 mg/mL group (34.7% vs 3.8%, $P < .05$).

The guideline working group performed a survey to 50 ART patients about their preference for LPS approaches and received 45 feedbacks: 49% of the responders chose a vaginal approach, 31% for intramuscular injection, and 20% for oral approach. Pros and cons of the three approaches of LPS are listed in Table 5

Recommendation 24

- A fetal deduction is suggested for women with advanced age and a twin pregnancy because it will decrease the risk of preterm birth and low birth weight neonate and increase the term pregnancy rate, the mean pregnancy duration, and neonatal birth weight. Patients should be comprehensively informed about the relevant risks if choosing not to have a fetal deduction. (2C)

"The technological specifications for assisted reproductive technology" revised and implemented by the Chinese Ministry of Health in 2003 regulated fetal deduction for a multiple pregnancies must be performed at a qualified facility. According to a 2015 Cochrane systematic review[115] (AMSTAR score = 11), there is no RCT on this topic yet. Other studies not specifically aimed at women with advanced age showed fetal deduction from twins to singleton could decrease the risk of preterm birth and low birth weight neonate and increase the term pregnancy rate, the mean pregnancy duration, and neonatal birth weight. A nonrandomized controlled trial in 2013[116] included 25 lean women with twin pregnancy after ART and found a lower miscarriage rate (8.3% vs 38.5%, $P > .05$), preterm birth rate (18.2% vs 100%, $P < .05$), and incidence of low neonatal birth weight (18.2% vs 88.9%, $P < .05$), and a higher term birth rate (81.8% vs 0%, $P < .05$), mean gestational age at delivery (38.5 ± 1.6 vs 32.8 ± 0.9, $P < .05$), and mean neonatal birth weight (2.5 ± 0.5 vs 1.7 ± 0.3, $P < .05$) after fetal deduction. A 2015 retrospective cohort study[117] ($n = 559$) demonstrated that fetal deduction from twins to singleton resulted in a significantly lower preterm birth rate before 37 gestational weeks (10% vs 43%, $P < .001$) and a lower risk of infant birth weight less than the 10% (23% vs 49%, $P < .001$). The results of another observational study from 2015[118] ($n = 416$) also showed a lower preterm birth rate, a longer duration of pregnancy, a higher infant birth weight, and a lower incidence of low birthweight infant (<2500 g) in the fetal deduction group (from twins to singleton, including spontaneous and iatrogenic reduction). But there was no significant difference in the miscarriage rate of the two groups.

Recommendation 25

- We suggest fetal deduction performed in the first or second trimester. Women with high-risk factors (≥40 years old, or with a history of recurrent miscarriage, or with a family history of hereditary disease, or with the risk of fetal inherently diseases) may wait till the second trimester to receive the fetal deduction. (2C)

The current available literature is mostly focusing on the timing of the fetal deduction for multi-pregnancies instead of twin pregnancies. A retrospective study in 2011 ($n = 123$) demonstrated the miscarriage rate after fetal deduction performed ≤8 gestational weeks is significantly lower (19.27% vs 64.29%, $P < .05$) than that of the patients who received fetal deduction after 8 weeks of gestation. Another retrospective study in 2012 found that the miscarriage rate of women who received fetal deduction at 12-13 gestational weeks is not different with that of women who received the procedure at 14-15 gestational weeks (14.5% vs 8.8%, $P > .05$) but lower than the miscarriage rate of women having fetal deduction at l6-24 gestational weeks (14.5% vs 31%, $P < 0.05$). In a 2016 retrospective cohort study ($n = 208$), fetal deduction performed at gestational week 6-8 led to a higher risk of arrested fetal development for the remaining fetus comparing to the 11-14 gestational week group (6% vs 0.8%, $P = .041$). Because pregnant women with a history of recurrent spontaneous abortion or delivering babies with congenital diseases, or women with a family history of hereditary diseases have a high risk of spontaneous miscarriage at the early pregnancy stage, performing fetal deduction at an early gestational week may be meaningless and may increase the risk of arrested fetal development for the remaining fetus on the contrary.[119] Furthermore, due to the limitation of early pregnancy ultrasound in detecting the potential fetal malformations, a "normal" fetus may be deducted instead of an "abnormal" one if performed in early

TABLE 5 Pros and cons of the three approaches of LPS

Approach	Advantages	Disadvantages
Intramuscular injection	• Has been used in the clinical setting for a long history, cheap, and complete absorption. • Can reach a relatively high plasma concentration, lasting for a long time, effectiveness and safety has been confirmed.	• Have to have the injection at the hospital repeatedly and low patient's compliance. • Progesterone preparation for intramuscular injection is oil soluble—absorbed slowly at the injection spot and may lead to the formation of local indurations or sterile cysts, which may further cause infection. • Repeat injection may lead to malabsorption and local accumulation of the medication, which may also result in skin swelling, tender spot accompanied by itching and pain.
Oral	• Good patient's compliance; less adverse reaction—easy to accept by the patients.	• Hepatic first-pass effect, more than 30 metabolites, may influence the secretion of prolactin and GnRH, and lead to hepatic function damage. • May result in obvious central nervous system symptoms such as dizziness and drowsiness. • Plasma progesterone concentration is monitored to infer whether LPS is sufficient; cannot reflect the progesterone concentration at endometrium; low bioavailability
Vaginal	• Can be administered by the patient, complete absorption, convenient, and painless. • Less local anaphylactic reaction. • The relatively longhalf-life and the small patient-to-patient variation in intaken ensure effective and stable absorption of the progesterone at the site of the endometrium.	• Patients often complain of an increased vaginal discharge and the vulva pruritus. • Relatively expensive.

pregnancy. As a result, many reproductive medicine centers suggest to postpone fetal deduction to the second trimester (11-24 gestational weeks) and to conduct an NT screening under ultrasound before the procedure to identify the target fetus. In conclusion, there is still no consensus in the timing of performing fetal deduction. Though, the timing of the fetal deduction is not the determining factor of patients' pregnancy outcomes. The timing of a fetal deduction procedure should be determined according to the clinical setting and the patients' situation.[120]

Other factors: Compared to singleton, multi-pregnancy causes a higher medical cost, mainly due to obstetric treatment, neonatal intensive care, and rehabilitation for children born with disabilities.[121] The perinatal care cost for twins, triplets, quadruplets is 2.1, 4.5, and 7 times of the expenses for a singleton, respectively, whereas the rehabilitation and education costs till 8 years old for newborns with low birth weight are 17 times higher than those with a healthy birth weight.[122]

The guideline working group surveyed 50 patients and received 47 feedbacks on this topic, which showed that 72% of the participants chose not to receive fetal deduction if they had twin pregnancy, 21% wanted to have a fetal deduction, and 7% preferred to leave the decision to the physicians.

4 | CONCLUSION

This guideline is the first Chinese guideline in reproductive medicine developed following the standard procedure of making a practice guideline. The clinical questions included are the most concerned clinical questions of Chinese physicians according to several rounds of investigation all over China. We also performed a comprehensive literature search and critical evaluation of evidence domestic and overseas, as well as a thorough survey and interview of Chinese patients' preference and value. The multi-disciplinary guideline working group finally came up with 25 recommendations with detailed explanations after in-depth discussions. Hence, this guideline will be able to provide guidance for Chinese physicians working in the area of reproductive medicine. However, the guideline working group has also realized there is a limitation of our guideline. Some of the recommendations are weak recommendations due to the lack of high-quality evidence; therefore, physicians have to make their judgment according to the reality of their clinics and patients' specific situation instead of following the recommendations rigidly. Meanwhile, we also suggest more high-quality studies in the following areas based on our findings in developing the guideline: (a) the diagnostic/classification criteria of DOR; (b) the appropriate timing of the fetal deduction for women with twins; (c) the effectiveness and safety of medications in improving ovarian reserve function, for example, DHEA and GH.

GUIDELINE EXPERT GROUP

Chief expert: Professor Shen Huan (Peking University People's Hospital)

Chief methodologist: Professor Chen Yaolong (Chinese GRADE Center/ Evidence-Based Medicine Center of Lanzhou University)

Members: Professor Sun Yingpu (Zhengzhou Medical University First Affiliated Hospital), Huang Guoning (Chongqing Maternal and Child Health Hospital), Shen Huan (Peking University People's

Hospital), Feng Yun (Shanghai Jiaotong University Ruijin Hospital), Zhu Yimin (Zhejiang University Maternity Hospital), Wang Xiaohong (The Fourth Military Medical University Tangdu Hospital), Yang Kehu (Chinese GRADE Center/ Evidence Based Medicine Center of Lanzhou University), Zhou Canquan (Sun Yet-sen University First Affiliated Hospital), Yang Dongzi (Sun Yet-sen University Sun Yet-sen Memorial Hospital), Sun Haixiang (Nanjing Drum Tower Hospital), Liang Xiaoyan (Sun Yet-sen University Sixth Affiliated Hospital), Deng Chengyan (Beijing Union Hospital), Ye Hong (Chongqing Maternal and Child Health Hospital), Zhang Xuehong (Lanzhou University First Affiliated Hospital), Xu Yang (Peking University First Hospital), Wang Liyun (Qinghai Province People's Hospital), Qin Aiping (Guangxi Medical University First Affiliated Hospital), Zhang Cuilian (Henan Province People's Hospital), Wu Qiongfang (Jiangxi Province Maternal and Child Health Hospital), Sun Xiaoxi (Fudan University Maternity Hospital), Zhang Yu (Xinjiang Shihezi University First Affiliated Hospital), Ma Yanping (Yunnan Province First People's Hospital), Gao Ying (Wuhan Union Hospital), Yang Yezhou (West China Maternity and Children Hospital), Li Yanping (Shandong Chinese Medicine University Affiliated Second Hospital), Hao Guimin (Hebei Medical University Second Hospital), Hu Linli (Zhengzhou Medical University First Affiliated Hospital), Li Pin (Xiamen Maternal and Child Health Hospital), Hao Cuifang (Shandong Liuhuangding Hospital), Wang Lei (Dalian Women and Children Medical Center), Quan Song (Nanfang Medical University Nanfang Hospital), Yao Yuanqing (301 Hospital), Lu Meisong (Haerbin Medical University First Affiliated Hospital), Mao Yundong (Nanjing Medical University First Affiliated Hospital), Zou Shuhua (Qindao Women and Children Health Care Center), Sun Wei (Shandong Chinese Medicine University Second Affiliated Hospital), Zhang Yunshan (Tianjin Central Maternity Hospital), Wang Liyan (Lanzhou University First Affiliated Hospital), Han Hongjing (Peking University People's Hospital), Liang Meiying (Peking University People's Hospital), Du Liang (Sichuan University West China Hospital), and Fu Min (Peking University People's Hospital)

ACKNOWLEDGMENTS

We thank the following experts for their contribution to our work: Professor Qingxue Zhang from Sun Yet-sen University Sun Yet-sen Memorial Hospital, Professor Shilin Chen from Nanfang Medical School Nanfang Hospital, Professor Aijun Zhang from Shanghai Ruijin Hospital, Professor Qifeng Lv from Shanghai 9th Hospital, Professor Ruizhi Liu from Jilin 1st Hospital, Professor Xiuxia Wang from China Medical University Shengjing Hospital, Professor Xiujuan Chen from Inner Mongolia Medical School-affiliated Hospital, Professor Xian Xu from Ningxia Medical School General Hospital, Professor Yuefan Kang from Fujian Maternity Hospital, Professor Yuanhua Huang from Hainan Medical School-affiliated Hospital, Professor Congrong Zhou from Guizhou Medical School-affiliated Hospital, Professor Ying Zhong, and Professor Lihong Geng from Sichuan Jinjiang Maternity Hospital. We also appreciate the clinicians taking the survey, patient representatives, and the guideline working group staff for their assistance.

DISCLAIMER

The development of this guideline was initiated by Chinese Society of Reproductive Medicine (CSRM). Based on the standard evidence-based guidelines developing method and the latest research evidence, a multidisciplinary group of experts discussed the included clinical questions comprehensively and reached a final consensus. However, the recommendations of the guideline do not represent the views of all members of CSRM, and there are still deficiencies and shortcomings of this edition of the guideline. Users of the guideline are welcome to provide their valuable suggestions and comments. We will make a relevant improvement in the next version. Besides, we solemnly declare that the opinions covered in this guideline are not allowed to be used for commercial promotion and publicity by any third party.

REFERENCES

1. Bushnick T, Garner R. *The Children of Older First-Time Mothers in Canada: Their Health and Development*. Ottawa, Canada: Statistics Canada; 2008.
2. Mathews TJ, Hamilton BE. Mean age of mothers is on the rise: United States, 2000–2014. *NCHS Data Brief*. 2016;(232):1-8.
3. Royal College of Obstetricians and Gynaecologists. RCOG statement on later maternal age. Available at: http://www.rcog.org.uk/what-we-do/campaigning-and-opinions/statement/rcog-statement-later-maternal-age. Accessed August 19, 2018.
4. Li YH, Wang YP, Dai L, et al. The trend of national advanced maternal age woman proportion in hospital-based surveillance. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2009;43(12):1073-1076.
5. Meng Q, Lin P. The differential investigation of the distribution of high-risk pregnant women before and after the rolling out of the "second-child" policy. *Matern Child Health Care China*. 2016;31(20):4266-4268.
6. Luo JM, Guo YW, Liao GX. The clinical analysis of the pregnancy outcomes and the delivery related risk factors of pregnant women with advanced maternal age. *China Pract Med*. 2016;11(24):87-88.
7. Khalil A, Syngelaki A, Maiz N, et al. Maternal age and adverse pregnancy outcome: a cohort study. *Ultrasound Obstet Gynecol*. 2013;42(6):634-643.
8. Usta IM, Nassar AH. Advanced maternal age. Part I: obstetric complications. *Am J Perinatol*. 2008;25(08):521-534.
9. Jo-Ann Johnson CA, Suzanne Tough CA. Delayed child-bearing. *J Obstet Gynaecol Can*. 2012;34(1):80-93.
10. Zegers-Hochschild F, Adamson GD, de Mouzon J, et al. The international committee for monitoring assisted reproductive technology (ICMART) and the world health organization (WHO) revised glossary on ART terminology, 2009. *Hum Reprod*. 2009;24(11):2683-2687.
11. Hu LL, Huang GN, Sun HX, et al. CSRM guideline for multifetal pregnancy reduction (2016). *J Reprod Med*. 2017;26(3):193-198.
12. Hu LL, Huang GN, Sun HX, et al. CSRM guideline for the use of ovulation induction drug (2016). *J Reprod Med*. 2017;26(4):302-307.
13. Penzias A, Bendikson K, Butts S, et al. Guidance on the limits to the number of embryos to transfer: a committee opinion. *Fertil Steril*. 2017;107(4):901-903.
14. Okun N, Sierra S, Committee G, et al. Pregnancy outcomes after assisted human reproduction. *J Obstet Gynaecol Can*. 2014;36(1):64-83.
15. National Collaborating Centre for Women's and Children's Health (UK). *Fertility: Assessment and Treatment for People with Fertility Problems*. London, England: Royal College of Obstetricians and Gynaecologists Press; 2013.

16. Myers ER, Mccrory DC, Mills AA, et al. Effectiveness of assisted reproductive technology (ART). *Evid Rep Technol Assess*. 2008;167 (167):1-195.
17. World Health Organization. *WHO Handbook for Guideline Development*. 2nd ed. Geneva, Switzerland: World Health Organization Press; 2014.
18. Jiang Z, Zhan S, Jia X, et al. Essential methods and procedures on how to develop and update clinical practice guidelines. *Natl Med J China*. 2016;96:250-253.
19. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182(18):1308-1311.
20. Chen Y, Yang K, Marušic A, et al. A reporting tool for practice guidelines in health care: the RIGHT statement. *Ann Intern Med*. 2017;166(2):128-132.
21. International Practice Guideline Registry Platform. http://www.guidelines-registry.org. Accessed August 19, 2018.
22. BJ S, JM G, GA W, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *Bmc Med Res Methodol*. 2007;7(2):1-7.
23. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928-d.
24. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
25. Wells GA, Shea BJ, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. *Appl Eng Agri*. 2014;18(6):727-734.
26. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines:1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
27. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ*. 2008;336(7652):1049-1051.
28. Vernooij RWM, Alonsocoello P, Brouwers M, et al. Reporting items for updated clinical guidelines: checklist for the reporting of updated guidelines (Checkup). *PLOS Med*. 2017;14(1):e1002207.
29. Hamilton BE, Martin JA, Osterman MJ, et al. Births: final data for 2014. *Natl Vital Stat Rep*. 2015; 64:1-64.
30. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet*. 2011;377(9774):1331-1340.
31. Morris JK, Vigan CD, Mutton DE, et al. Risk of a Down syndrome live birth in women 45 years of age and older. *Prenat Diagn*. 2005;25(4):275-278.
32. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ*. 2005;330(7491):565.
33. Heffner LJ. Advanced maternal age–how old is too old. *N Engl J Med*. 2004;351(19):1927-1929.
34. Sun Y, Zhu YM. Infertile couples with advanced age: a dilemma for assisted reproductive technolog. *Chin J Fam Planning Gynecol*. 2014;6(8):1-3.
35. Qiao J, Yang R. The assisted reproductive technology (ART) outcomes of women with advanced maternal age. *Chin J Pract Obstet Gynecol*. 2017;33(1):64-67.
36. Yang YF, Fu JM, Ruan XY. The age distribution and follow up of uterine myorna. *J Pract Obstet Gynecol*. 2008;24(5):299-301.
37. Timofeev J, Reddy UM, Huang CC, et al. Obstetric complications, neonatal morbidity, and indications for cesarean delivery by maternal age. *Obstet Gynecol*. 2013;122(6):1184-1195.
38. America Heart Association News. Pregnancy in older age increases stroke, heart attack risk years later. AHA/ASA Newsroom.February 17, 2016. http://newsroom.heart.org/news/pregnancy-in-older-age-increases-stroke-heart-attack-risk-years-later. Accessed August 19, 2018.
39. Xue J, Chen LZ, Xue L, et al. Meta-analysis of risk factors for childhood cerebral palsy during pregnancy. *Chin J Contemp Pediatr*. 2013;15(7):535-540.
40. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee. Female age-related fertility decline: Committee opinion no. 589. *Fertil Steril*. 2014;101(3):663-664.
41. National Collaborating Centre for Women's and Children's Health (UK). Fertility: assessment and treatment for people with fertility problems: NICE guideline. *Br J Gen Pract* 2013, 64(618): 1-555.
42. Reproductive Endocrinology and Infertility Committee. Advanced reproductive age and fertility. *J Obstet Gynaecol Can*. 2011;33(11): 1165-1175.
43. Chinese Medical Doctor Association Reproductive Medcine Specialized Committe. Guideline for diagnosis and treatment of infertility in advanced age women. *Reprod Contracept*. 2017;37(2): 87-100.
44. National Center for Chronic Disease Prevention and Health Promotion &Division of Reproductive Health. *2015 assisted reproductive technology fertility clinic success rates report*. Atlanta, GA: National Center for Chronic Disease Prevention and Health Promotion &Division of Reproductive Health. https://www.cdc.gov/art/reports/2015/fertility-clinic.html. Accessed August 19, 2018.
45. Zhang YF, Sun GX. A meta analysis of the risk factors during pregnancy for low birth weight neonate. *Matern Child Health Care China*. 2016;31(5):1115-1118.
46. Liang L, Chen XJ. Analysis of embryonic development and pregnancy outcomes in elderly infertile women undergoing different assisted reproductive technology. *Chin J Obstet Gynecol Pediatr*. 2014;10(6):770-773.
47. Xie YQ, Xiao H, Liu M, et al. An analysis of the psycological health related factors for infertile women with advanced age and receiving assisted reproductive technology (ART) for a second child. *Reprod Contracept*. 2016;36(12):1031-1035.
48. Kelly-Weeder S and Cox CL. The impact of lifestyle risk factors on female infertility. *Women Health* 2006;44(4):1-23.
49. Faddy MJ, Gosden RG, Gougeon A. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Hum Reprod*. 1992;7(10):1342-1346.
50. Liu JL, Lin CL, Meng ZM, et al. Clinical study of age and sex hormone levels in the prediction of ovarian reserve. *Pub Med Forum Mag*. 2013;17(1):3-4.
51. Steiner AZ, Pritchard D, Stanczyk FZ, et al. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. *J Am Med Assoc*. 2017;318(14):1367-1376.
52. Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. *Fertil Steril* 2015;103(03):e9-e17.
53. Zhang HH, Xu PY, Wu J, et al. Dehydroepiandrosterone improves follicular fluid bone morphogenetic protein-15 and accumulated embryo score of infertility patients with diminished ovarian reserve undergoing in vitro fertilization: a randomized controlled trial. *J Ovarian Res*. 2014;7(1):93.
54. Song HL, Guo YH, Sun YP, et al. Effect of growth hormone on the IVF outcome of the patients decreased ovarian reserve at different age. *Reprod Contracept*. 2013;33(1):58-62.
55. Kara M, Aydin T, Aran T, et al. Does dehydroepiandrosterone supplementation really affect IVF-ICSI outcome in women with poor ovarian reserve. *Eur J Obstet Gynecol Reprod Biol*. 2014;173: 63-65.
56. Barad D, Brill H, Gleicher N. Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. *J Assist Reprod Genet*. 2007;24:629-634.
57. Chen SL. Evaluation on ovarian reserve. *J Int Reprod Health/Fam Plan*. 2009;28(5):281-286.

58. Broer SL, Broekmans FJ, Laven JS, et al. Anti-mullerian hormone: ovarian reserve testing and its potential clinical implications. *Hum Reprod Update*. 2014;20(5):688-701.
59. Durlinger AL, Gruijters MJ, Kramer P, et al. Anti-mullerian hormone inhibits initiation of primordial follicle growth in the mouse ovary. *Endocrinology*. 2002;143(3):1076-1084.
60. Tal R, Tal O, Seifer BJ, et al. Antimullerian hormone as predictor of implantation and clinical pregnancy after assisted conception: a systematic review and meta-analysis. *Fertil Steril*. 2015;103(1):119-130.
61. Yang ZX, Zhu QY, Zhao FX, et al. Value of serum anti-müllerian hormone levels of early follicular phase for predicting low ovarian response. *J Pract Obstet Gynecol*. 2016;32(08):593–596.
62. Toner JP, Seifer DB. Why we may abandon basal follicle-stimulating hormone testing: a sea change in determining ovarian reserve using antimüllerian hormone. *Fertil Steril*. 2013;99:1825.
63. Eldar-Geva T, Ben-Chetrit A, Spitz IM, et al. Dynamic assays of inhibin B, anti-Mullerian hormone and estradiol following FSH stimulation and ovarian ultrasonography as predictors of IVF outcome. *Hum Reprod*. 2005;20:3178-3183.
64. McIlveen M, Skull JD, Ledger WL. Evaluation of the utility of multiple endocrine and ultrasound measures of ovarian reserve in the prediction of cycle cancellation in a high-risk IVF population. *Hum Reprod*. 2007;22:778-785.
65. Hall JE, Welt CK, Cramer DW. Inhibin A and inhibin B reflect ovarian function in assisted reproduction but are less useful at predicting outcome. *Hum Reprod*. 1999;14:409-415.
66. Creus M, Penarrubia J, Fabregues F, et al. Day 3 serum inhibin B and FSH and age as predictors of assisted reproduction treatment outcome. *Hum Reprod*. 2000;15:2341-2346.
67. Smeenk JM, Sweep FC, Zielhuis GA, et al. Anti-mullerian hormone predicts ovarian responsiveness, but not embryo quality or pregnancy, after in vitro fertilization or intracyoplasmic sperm injection. *Fertil Steril*. 2007;87:223-226.
68. Committe on Gynecologic Practice. Committee opinion no. 618: ovarian reserve testing. *Obstet Gynecol*. 2015, 125(1):268.
69. Kwe J, Ehing ME, Sehats R, McDonnell J, Lambalk CB. Ovarian volume and antral follicle count for the prediction of low and hyper responders with in vitro fertilization. *Reprod Biol Endocrinol*. 2007;15(5):9-18.
70. Frattarelli JL, Lauria-Costab DF, Miller BT, et al. Basal antral follicle number and mean ovarian diameter predict cycle cancellation and ovarian responsiveness in assisted reproductive technology cycles. *Fertil Steril*. 2000;74:512-517.
71. Qin JC, Fan L, Qin AP. The effect of dehydroepiandrosterone (DHEA) supplementation on women with diminished ovarian reserve (DOR) in IVF cycle: evidence from a meta-analysis. *J Gynecol Obstet Hum Reprod*. 2017;46(1):1-7.
72. Ji J, Ju XQ, Wang JF, et al. Effectiveness of dehydroepiandrosterone in poor ovarian responders undergoing in vitro fertilization: a meta-analysis of randomized controlled trials. *Int J Clin Exp Med*. 2016;9(11):20835-20845.
73. Li J, Yuan H, Chen Y, et al. A meta-analysis of dehydroepiandrosterone supplementation among women with diminished ovarian reserve undergoing in vitro fertilization or intracytoplasmic sperm injection. *Int J Obstet Gynaecol*. 2015;131(3):240-245.
74. Dong J, Xu WM, Dong L, et al. Systematic evaluation of effect of usage of dehydroepiandrosterone before IVF on pregnancy outcome in women with diminished ovarian reserve. *J Reprod Med*. 2015;24(6):436-443.
75. Panjari M, Bell RJ, Jane F, et al. A randomized trial of oral DHEA treatment for sexual function, well-being, and menopausal symptoms in postmenopausal women with low libido. *J Sex Med*. 2009;6(9):2579-2590.
76. Kaaks R, Berrino F, Key T, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst*. 2005;97(10):755-765.
77. Li XL, Wang L, Lv F, et al. The influence of different growth hormone addition protocols to poor ovarian responders on clinical outcomes in controlled ovary stimulation cycles: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96(12):e6443.
78. Harper K, Proctor M, Hughes E, et al. Growth hormone for in vitro fertilization. *Cochrane Database Syst Rev*. 2009;(3):CD000099.
79. Veltman-Verhulst SM, Hughes E, Ayeleke RO, Cohlen BJ. Intrauterine insemination for unexplained subfertility. *Cochrane Database Syst Rev*. 2016;19(2). https://doi.org/10.1002/14651858
80. Cao JY, Li AB, Niu T, et al. Effectiveness of natural cycle and ovulation induction cycle in intrauterine insemination: a meta analysis. *Chin J Birth Health Heredity*. 2015(2):98-101.
81. Sun J, Quan XZ, Xie MX, et al. Analysis on clinical factors related to artificial insemination with husband sperm in 1 382 cycles. *Matern Child Health Care China*. 2011;26(11):1658-1660.
82. Chen H, Zhou M, Li QY, et al. The analysis of relevant factors influencing on the clinicalpregnancy rate of intrauterine insemination with husband sperm. *Chin J Birth Health Heredity*. 2012;20(1):98–101.
83. Lu WY, Liu XR, Huang YH, et al. Analysis of clinical factors affecting pregnancy rate of intrauterine artificial insemination from 718 cycles. *J Hainan Med Univ*. 2006;12(4):310-313.
84. Goldman MB, Thornton KL, Ryley D, et al. A randomized clinical trial to determine optimal infertility treatment in older couples: the forty and over treatment trial (FORT-T). *Fertil Steril*. 2014;101(6):1574-1581.
85. Hill MJ, Levens E D, Levy G, et al. The use of recombinant luteinizing hormone in patients undergoing assisted reproductive techniques with advanced reproductive age: a systematic review and meta-analysis. *Fertil Steril*. 2012;97(5):1108-1104.
86. Xiong F, Zhou P, Hu LQ, et al. The role of recombinant luteinizing hormone in ovarian hyperstimulation for patients with normal ovarian reserve. *Matern Child Health Care China*. 2016;31(2):336-338.
87. Yang J, Wu SQ. Effect of luteinizing hormone supplementation in middle or late follicle phase on the outcome of in vitro fertilization-embryo transfer of long protocol controlled ovarian hyperstimulation. *Int Med Health Guid News*. 2016;22(19):2929-2933.
88. Vuong TNL, Phung HT, Ho MT. Recombinant follicle-stimulating hormone and recombinant luteinizing hormone versus recombinant follicle-stimulating hormone alone during GnRH antagonist ovarian stimulation in patients aged≥ 35 years: a randomized controlled trial. *Hum Reprod*. 2015;30(5):1188-1195.
89. Mochtar MH, Danhof NA, Ayeleke RO, et al. Recombinant Luteinizing Hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles. *Cochrane Database Syst Rev*. 2017;24(5):CD005070.
90. Chen X, Geng L, Li H. Clinical outcomes and economic analysis of two ovulation induction protocols in patients undergoing repeated IVF/ICSI cycles. *J Southern Med Univ*. 2014;34(4):563-567.
91. Boulet SL, Mehta A, Kissin DM. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. *J Am Med Assoc*. 2015;313(3):255-263.
92. Rumste MMV, Evers JL, Farquhar C. Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility. *Cochrane Database Syst Rev*. 2003;2(2):CD001301.
93. Wen J, Jie J, Ding C, et al. Birth defects in children conceived by invitro fertilization and intracytoplasmic sperm injection: a meta-analysis. *Fertil Steril*. 2012;97(6):1331-1337.
94. Abramowicz JS, Kossoff G, Maršál K, et al. International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). *Ultrasound Obstet Gynecol*. 2000;16(6):594–596.
95. Harton G, Braude P, Lashwood A, et al. ESHRE PGD consortium best practice guidelines for organization of a PGD centre for

PGD/preimplantation genetic screening. *Hum Reprod*. 2010;26(1): 14-24.
96. Okun N, Sierra S, Wilson RD, et al. Pregnancy outcomes after assisted human reproduction. *J Obstet Gynaecol Can*. 2014;36(1):64-83.
97. Mastenbroek S, Twisk M, Van der VF, Repping S. Preimplantation genetic screening: a systematic review and meta-analysis of RCTs. *Hum Reprod Update*. 2011;19(2):454-466.
98. Chen M, Wei S, Hu J, Quan S. Can comprehensive chromosome screening technology improve IVF/ICSI outcomes? A meta-analysis. *PLoS One*. 2015;10(10):e0140779.
99. Yang Z, Lin J, Zhang J, et al. Randomized comparison of next-generation sequencing and array comparative genomic hybridization for preimplantation genetic screening: a pilot study. *BMC Med Genomics*. 2015;8(1):30.
100. Lai HH, Chuang TH, Wong LK, et al. Identification of mosaic and segmental aneuploidies by next-generation sequencing in preimplantation genetic screening can improve clinical outcomes compared to array-comparative genomic hybridization. *Mol Cytogenet*. 2017;10(1):14.
101. Xu YW, Huang GN, Sun HX, et al. CSRM guidelines for next generation sequencing-based PGD/PGS. *J Reprod Med*. 2017;26(5): 391-398.
102. Huang J, Ma CH. Technique and standard of preimplantation ge. *Chin J Pract Gynecol Obstet*. 2015;31(09):814-817.
103. Sun YP, Li G. [The safety of PGD/PGS] [C]// 2014. The annual meeting of Zhejiang Province Family Planning and Reproduction Medicine. 2014.
104. Pandian Z, Marjoribanks J, Ozturk O, Serour G, Bhattacharya S. Number of embryos for transfer following in vitro fertilisation or intracytoplasmic sperm injection. *Cochrane Database Syst Rev*. 2013;29(7). https://doi.org/10.1002/14651858.CD003416.
105. McLernon DJ, Harrild K, Bergh C, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *BMJ*. 2010;341:c6945.
106. Kissin DM, Kulkarni AD, Kushnir VA, Jamieson DJ, National ART Surveillance System Group. Number of embryos transferred after in vitro fertilization and good perinatal outcome. *Obstet Gynecol*. 2014;123(2 Pt 1):239-247.
107. Practice Committee of the American Society for Reproductive Medicine, Practice Committee of the Society for Assisted Reproductive Technology. Guidance on the limits to the number of embryos to transfer: a committee opinion. *Fertil Steril*. 2017;107(4):901-903.
108. NICE. *Fertility problems: assessment and treatment (CG156)[J]*. London, England: NICE; 2016.
109. Lawlor DA, Nelson SM. Effect of age on decisions about the numbers of embryos to transfer in assisted conception: a prospective study. *Lancet*. 2012;379(9815):521-527.
110. Xue YM, Tong XM, Zhang SY. Effect of vaginal gel and intramuscular progesterone for luteal phase support in in vitro fertilization-embryo transfer: a meta analysis. *Reprod Contracept*. 2015;35(4):252-258.
111. Zargar M, Saadati N, Ejtahed MS. Comparison the effectiveness of oral dydrogesterone, vaginal progesterone suppository and progesterone ampule for luteal phase support on pregnancy rate during ART cycles[J]. *Int J Pharm Res Allied Sci*. 2016;5(3):229-236.
112. Saharkhiz N, Zamaniyan M, Salehpour S, et al. A comparative study of dydrogesterone and micronized progesterone for luteal phase support during in vitro fertilization (ivf) cycles. *Gynecol Endocrinol*. 2016;32(3):213-217.
113. Wei Z, Sun J. Reflections on the medication safety for progesterone injection events. *China Pharm*. 2016;27(13):1749-1751.
114. Zhang HY. The local side effect of intramuscular progesterone injection and its nursing stratetigies. *Guid China Med*. 2012;10(21):672-673.
115. Dodd JM, Dowswell T, Crowther CA. Reduction of the number of fetuses for women with a multiple pregnancy. *Cochrane Database Syst Rev*. 2015:4(11). https://doi.org/10.1002/14651858.CD003932
116. Wang YY, Zhao J, Zhang P, et al. The influence of fetal deduction from twins after assisted reproductive technology (ART) to singleton on the pregnancy outcomes for lean women. *Matern Child Health Care China*. 2013;28(26):4343-4344.
117. Gupta S, Fox NS, Feinberg J, Klauser CK, Rebarber A. Outcomes in twin pregnancies reduced to singleton pregnancies compared with ongoing twin pregnancies. *Am J Obstet Gynecol*. 2015;213(4):580. e5.
118. Pan YD. *The Impact of Multiple Pregnancy Reduction on Obstetric Outcome and Children Cognition after Assisted Reproductive Technology*. Hangzhou, China: Zhejiang University; 2015.
119. Dickey RP. Embryonic loss in iatrogenic multiples. *Obstet Gynecol Clin North Am*. 2005;32(1):17-27.
120. Zhu XF. The relationship between the timing of fetal deduction and the pregnancy outcomes. *China Pract Med*. 2009;4(30):201-202.
121. Seoud MA, Toner JP, Kruithoff C, Muasher SJ. Outcome of twin, triplet, and quadruplet in vitro fertilization pregnancies: the Norfolk experience. *Fertil Steril*. 1992;57(4):825.
122. Stevenson RC, Pharoah PO, Stevenson CJ, Mccabe CJ, Cooke RW. Cost of care for a geographically determined population of low birthweight infants to age 8–9 years. II. Children with disability. *Arch Dis Child Fetal Neonatal Ed*. 1996;74(2):F118.

How to cite this article: Jiang L, Chen Y, Wang Q, et al. A Chinese practice guideline of the assisted reproductive technology strategies for women with advanced age. *J Evid Based Med*. 2019;12:167–184. https://doi.org/10.1111/jebm.12346

APPENDIX: THE FLOW CHART OF THE GUIDELINE DEVELOPMENT PROCESS