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ARTICLE

How time to healthy singleton delivery could affect decision-making during infertility treatment: a Delphi consensus

BIOGRAPHY

Ernesto Bosch was born in Philadelphia, USA, in 1968. He has worked at the Instituto Valenciano de Infertilidad since 2000, published 52 papers in peer-reviewed journals and more than 50 book chapters in the field of IVF, and has given over 200 lectures at international meetings around the world.

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KEY MESSAGE:

This Delphi consensus agreed that time to healthy singleton delivery is an important factor when making treatment decisions with all patients undergoing infertility treatment, especially those aged >35 years. However, more research is needed on the impact of treatment choices on time to healthy singleton delivery.

ABSTRACT

Research question: How might time to healthy singleton delivery affect decision-making during infertility treatment?

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Declaration: All authors received an honorarium for participation in this Delphi consensus, but no money was received for authoring this manuscript. Outside the submitted work: EB has received personal fees as honoraria for speaking bureaus and advisory boards from Ferring Pharmaceuticals, Merck, MSD, Finox and Roche Diagnostics. HY has received honoraria for lectures and preceptor courses, and unrestricted research grants from Merck. NPP has received research grants and honoraria for lectures from Merck Serono, MSD, Ferring Pharmaceuticals, Besins International and Roche Diagnostics. FMU has received honoraria for lectures and unrestricted research grants from Merck, MSD, Ferring and Excemed. JAGV has received unrestricted research grants from Merck, MSD and Ferring. SL and TDH are employees of Merck KGaA, Darmstadt, Germany. PH has received unrestricted research grants and honoraria for lectures from MSD, Merck, Ferring and IBSA. CB, RF, CAP, DS, ABC have nothing to disclose.

KEYWORDS

ART
Assisted reproductive technology
Delphi consensus
IVF
Time to healthy singleton delivery

Design: This was a Delphi consensus investigating expert opinion that comprised three steps. In Step 1, 12 experts developed statements. In Step 2, 27 experts (including 12 from Step 1) voted (online survey) on their agreement/disagreement with each statement (providing reasons). Consensus was reached if ≥66% of participants agreed/disagreed. Statements not reaching consensus were revised and the process repeated until consensus was achieved. In Step 3 details of the final agreed statements were communicated.

Results: Twelve statements were developed, and consensus (agreement) was reached on all after one round of voting.

Conclusions: Time to healthy singleton delivery should be taken into consideration when making decisions related to infertility treatment, and it is important that fertility treatment is provided in a timely manner, avoiding over- or under-treatment. In all subfertile women <40 years old, IVF outcomes could be optimized by performing up to six single-embryo transfers and certain procedures might reduce time to healthy singleton delivery. These procedures include preimplantation genetic testing for aneuploidies, frozen replacement cycles immediately after failed fresh cycles and use of gonadotrophin-releasing hormone antagonists. Finally, the number of oocytes retrieved should be maximized to increase cumulative live birth rate.

INTRODUCTION

Time to healthy singleton delivery is an important consideration when making treatment decisions for assisted reproductive technologies (ART) and should be included as an aspect of the decision-making process for women of all ages. Clearly, considerations of time are of particular importance for women aged >35 years, owing to the steady decline in fertility observed with age, which is gradual from 30–35 years and accelerates thereafter (*American Society for Reproductive Medicine, 2014*). Increased aneuploidy rates are also observed in women aged >35 years, further impacting fertility (*Franasiak et al., 2014*). This decline in fertility results in a lower cumulative live birth rate (*American Society for Reproductive Medicine, 2014*), and as the mean age at which women are seeking fertility treatment is increasing (*ESHRE Capri Workshop Group, 2010*), this issue is of growing importance. It should, however, be noted that chronological age might not accurately reflect 'biological age' for fertility outcomes. Furthermore, up to 50% of patients discontinue IVF treatment by the time of a second failed cycle, with about 26% discontinuing after a single failed cycle in one study (*Troude et al., 2014*). Discontinuation may relate to economic concerns relating to the cost of treatment and psychosocial factors, including loss of hope of success and the psychological burden of treatment (*Lande et al., 2015; Van Dongen et al., 2015*). This risk of discontinuation has been observed to be associated with no embryo transfer in a prior cycle and factors that reduce the likelihood of successful IVF treatment, including advanced chronological age or diminished ovarian reserve (*Troude et al., 2014*). This high discontinuation rate highlights the need to maximize the live birth rate for each treatment cycle. Furthermore, because the risk for treatment failure increases with age, and each failure reduces the window of opportunity for conception, time to healthy singleton delivery can become increasingly important as the duration of treatment increases (*Kocourkova et al., 2014*).

The UK National Institute for Health and Clinical Excellence (NICE) recommends that all subfertile women <40 years of age should receive up to three IVF treatment cycles funded by the NHS (*National Institute for Health and Care Excellence, 2013*). A study in the UK observed a median time interval between the first and second treatment cycle of 11 months and between the second and third treatment cycles of 10 months (*Goswami et al., 2013*). Based upon these time intervals, it would take almost 2 years for couples to complete the full course of NHS-funded treatment (*Goswami et al., 2013*). During the time between treatment cycles, there is the possibility that people will decide to discontinue treatment and as maternal age steadily increases the likelihood of a successful outcome will decrease. Furthermore, studies have demonstrated that the time interval can be decreased by performing IVF as quickly as possible and repeating IVF as soon as possible in the case of failure, so that three IVF cycles could be attempted in 153 days (*Reichman et al., 2013*). This is possible because no advantage has been observed from having an interval of two or more menstrual cycles between IVF cycles compared with having only one (*Reichman et al., 2013*). Thus time to complete an IVF programme can be reduced if practice is modified based on the most up-to-date research, using a patient-tailored approach. This example is based on the optimization of a single aspect of IVF treatment and if fertility specialists could improve every aspect of IVF in a similar manner, it seems likely that IVF success rates could be increased (*Di Spiezio Sardo et al., 2016*). This evidence highlights that 'time to pregnancy' and 'time to healthy singleton delivery' are essential concepts for human reproduction (*te Velde et al., 2000*) and explains the increasing interest and clinical relevance of shortening treatment times and the overall time to a successful outcome. However, at present, there is no generally agreed upon, specific, shorter duration of time to healthy singleton delivery that is considered clinically relevant. Nevertheless, any intervention that may shorten the time to pregnancy should be considered beneficial.

Despite the importance of these factors, there is currently no consensus on specific approaches for optimizing ART treatment with the aim of shortening the time to a healthy singleton delivery. A Delphi consensus was therefore conducted to gather and evaluate expert opinion on how time to a healthy singleton delivery might impact the individualization of ART treatment, and also how treatment protocols and/or procedures might be optimized to shorten the time to healthy singleton delivery (*Diamond et al., 2015*).

TABLE 1 PARTICIPANTS

Name	Country	Step 1	Step 2	Step 3	
		12 May 2016 WebEx meeting		20 September 2016 WebEx meeting	22 September 2016 WebEx meeting
Peter Humaidan	Denmark	X	X		
Ernesto Bosch	Spain	X	X	X	X
Brian Berger	USA	X	X	X	
Carlo Bulletti	Italy	X	X		X
Alan B Copperman	USA	X	X	X	
Renato Fanchin	France	X	X		
Hakan Yarali	Turkey	X	X	X	
Carlos A. Petta	Brazil	X	X		X
Nikolaos P Polyzos	Spain	X	X	X	
Daniel Shapiro	USA	X	X		X
Filippo Maria Ubaldi	Italy	X	X		X
Juan Garcia Velasco	Spain	X	X		X
Jose Bellver	Spain		X	X	
Francisco Arredondo	USA		X	X	
Joaquín Llacer	Spain		X	X	
Amber Cooper	USA		X	X	
Didier Dewailly	France		X		
Alfredo Guillen	Spain		X	X	
Christophe Blockeel	Belgium		X		
Pedro Barri	Spain		X		
Rui Ferriani	Brazil		X		X
Catherine Avril	France		X		
Paolo Levi Setti	Italy		X		
Anja Bisgaard Pinborg	Denmark		X		
Andrea Borini	Italy		X		
Bülent Urman	Turkey		X		
Semra Kahraman	Turkey		X		

MATERIALS AND METHODS

The Delphi consensus was developed over three steps (TABLE 1 and FIGURE 1) coordinated by a healthcare consulting and training company (Sanitanova Srl, Milan, Italy), with the aim of generating, refining and achieving consensus on statements relating to time to healthy singleton delivery. The consensus was initiated and funded by Merck KGaA, who did not participate in the development of the statements or in any of the meetings or discussions involved in developing the Delphi consensus. However, the Merck authors developed the overall concept to be discussed by the Delphi TTP Consensus Group and were involved in the development of the manuscript, critically revising it for important intellectual content, especially in the Background and Discussion sections. The statements were developed during Step 1, based on an evaluation of the most up-to-date scientific literature relating to time to healthy singleton delivery, in addition to expert opinion. In Step 2, the statements from Step 1 were voted on by a larger panel of experts with the aim of achieving consensus opinions on each statement and the votes of all panel members were weighted equally. The outcome of Step 2 was then communicated to all participants during Step 3, with individual input anonymized to better enable open discussion and critique.

Participants

Step 1 involved a panel of 12 experts who were selected and invited to participate by Sanitanova Srl on the basis of their publication record related to 'time to pregnancy' and relevant contributions to international medical congresses and meetings (TABLE 1). Each of these 12 experts proposed two additional experts based on their clinical experience with ART, who were invited to participate in the subsequent steps of the consensus process. Of the 24 experts invited, 15 participated in Step 2, resulting in a total of 27 experts being involved in the consensus (TABLE 1). Dr Humaidan chaired Step 1 and Dr Bosch chaired Steps 2 and 3.

Statements

Step 1

Step 1 aimed to develop statements relating to time to healthy singleton

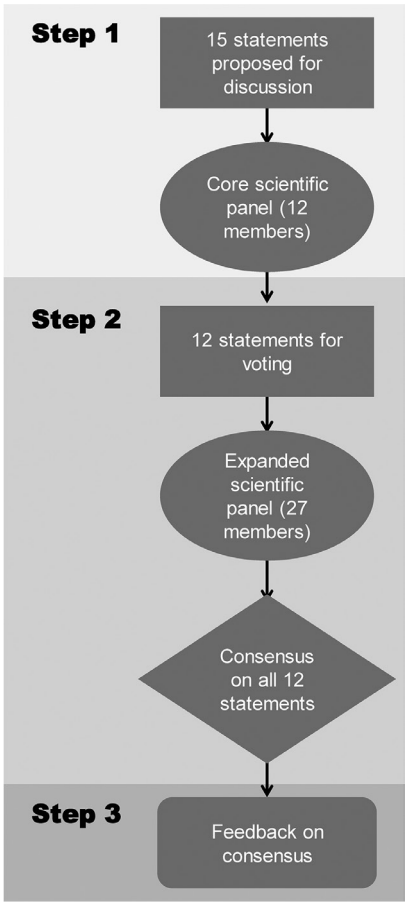

FIGURE 1 The three steps of the Delphi consensus process. Before Step 1, 15 statements (accompanied by supporting references) were generated by the coordinating agency in collaboration with the chairman of the panel (Dr Humaidan) to stimulate discussion. In Step 1, a core panel of 12 experts developed 12 statements relating to time to healthy singleton delivery based on discussion of the 15 statements initially proposed. In Step 2, an expanded panel of 27 experts voted via an online survey on their level of agreement with the 12 statements until consensus was reached (66% agreed). In Step 3, full details of the final agreed statements were communicated to the participants.

delivery that would be voted on during Step 2. Fifteen statements (accompanied by supporting references) were initially generated by the coordinating agency in collaboration with the chairman of the panel (Dr Humaidan), based on an evaluation of the most up-to-date scientific literature relating to time to healthy singleton delivery. These initial statements were intended to stimulate discussion and act as a starting point for the development of the statements to be voted on during Step 2. The 12 experts participating in Step 1 then discussed these statements during a web conference. During this web conference the panel could add, remove or amend the proposed statements, including the addition or removal of supporting references, with the final selection of statements to be considered in Step 2 decided by consensus among the 12 experts. The statements, with their supporting references, were subsequently circulated to the 12 participants by e-mail for further comment and/or approval. There was no predefined number of statements to be included in the Delphi consensus.

Step 2

Step 2 aimed to develop a consensus on the statements developed during Step 1. An online survey containing the statements agreed upon by the 12 experts during Step 1 was circulated to the 27 participants in Step 2. Each participant then rated their level of agreement with each statement using a five-item Likert scale: 1 = absolutely disagree; 2 = disagree; 3 = agree; 4 = more than agree; 5 = absolutely agree (*Concolino et al., 2014; Girolomoni et al., 2015*). Participants were also asked to provide the main reason (free text) for their chosen level of agreement or disagreement.

Consensus was considered to have been achieved if the proportion of participants either disagreeing with the statement (responding 1 or 2) or agreeing with the statement (responding 3, 4 or 5) exceeded 66% (*Concolino et al., 2014; Girolomoni et al., 2015*). If the proportion of participants either agreeing or disagreeing with a statement did not exceed 66%, that statement would be revised according to the feedback received and another survey initiated including only the statements not reaching consensus. This process would be repeated, with the statements being revised, until consensus was reached for every statement.

Step 3

Once consensus was achieved for all statements, web conferences were arranged to provide feedback to participants. These web conferences were not compulsory to attend and were intended to communicate the outcome of Step 2 to participants (i.e. to report

TABLE 2 CONSENSUS STATEMENTS

	References
Age and time to healthy singleton delivery	
1. It is crucial that fertility treatment is managed in a timely manner that avoids over- or under-treatment	*American Society for Reproductive Medicine (2014)*
2. In all subfertile women <40 years old, an optimal cumulative IVF outcome could be obtained by performing up to six single-embryo transfers	*Gnoth et al. (2003), Goswami et al. (2013)*
3. Patient age does not affect the cumulative live birth rate in oocyte donation cycles if oocyte donors are aged 18–34 years old	*Garrido et al. (2012)*
Procedures that might optimize time to healthy singleton delivery	
4. Preimplantation genetic testing for aneuploidies can decrease the aneuploidy rate and shorten time to pregnancy and time to healthy singleton delivery	*Ubaldi et al. (2015)*
5. Preimplantation genetic testing for aneuploidies with comprehensive chromosomal screening can increase both clinical and sustained implantation rates	*Dahdouh et al. (2015)*
6. In women >35 years old, elective SET combined with enhanced embryo selection using preimplantation genetic testing for aneuploidies can reduce the multiple pregnancy rate while maintaining the cumulative success rate of an IVF programme	*Ubaldi et al. (2015)*
7. A frozen–thawed replacement transfer cycle could be considered immediately after a failed fresh transfer cycle, as this results in a similar clinical pregnancy rate to a frozen–thawed transfer cycle postponed to a later time	*Santos-Ribeiro et al. (2016)*
8. DuoStim (using FSH and LH in combination with a GnRH antagonist) could be used in patients with reduced ovarian reserve	*Ubaldi et al. (2016)*
Oocyte retrieval and time to healthy singleton delivery	
9. The cumulative live birth rate (including live births from fresh and frozen–thawed embryos) significantly increases with the number of oocytes retrieved	*Drakopoulos et al. (2016)*
GnRH antagonist use and time to healthy singleton delivery	
10. The use of a GnRH antagonist may shorten the treatment period (i.e. fewer stimulation days) with lower FSH consumption and a reduced number of injections	*Devroey et al. (2009)*
11. In normal responder patients GnRH antagonists have similar efficacy to GnRH agonists	*Al-Inany et al. (2016)*
12. A GnRH agonist can be used to trigger ovulation in a GnRH antagonist cycle, significantly decreasing the risk of cycle cancellation and ovarian hyperstimulation syndrome in normal responder patients	*Al-Inany et al. (2016)*

GnRH = gonadotrophin-releasing hormone; SET = single-embryo transfer.

on the level of consensus with each statement), and the statements could not be amended at this stage.

RESULTS

Twelve statements, with supporting references (*Al-Inany et al., 2016; American Society for Reproductive Medicine, 2014; Dahdouh et al., 2015; Devroey et al., 2009; Drakopoulos et al., 2016; Garrido et al., 2012; Gnoth et al., 2003; Goswami et al., 2013; Santos-Ribeiro et al., 2016; Ubaldi et al., 2015*) (TABLE 2) were voted on during Step 2 by 27 participants. Consensus was reached on all statements after the first round of voting, with participants agreeing with all statements (FIGURE 2). The feedback web conferences were voluntarily attended by 16 participants. The 12 statements included in this Delphi consensus can be categorized into four topics according to their general focus. These topics are: age and time to healthy singleton delivery; procedures that might optimize time to healthy singleton delivery; oocyte retrieval and time to healthy singleton delivery; gonadotrophin-releasing hormone (GnRH) antagonist use and time to healthy singleton delivery.

Age and time to healthy singleton delivery

1. It is crucial that fertility treatment is managed in a timely manner that avoids over- or under-treatment (*American Society for Reproductive Medicine, 2014*)

Female age is implicitly linked to time to healthy singleton delivery (*American Society for Reproductive Medicine, 2014*). In general, the decline in fertility is gradual until the age of about 35 years, after which the decline accelerates until menopause occurs (*Broekmans et al., 2009; Hansen et al., 2008*). This suggests that the longer patients are either waiting for or undergoing ART treatment, the worse their prognosis is likely to become (*American Society for Reproductive Medicine, 2014; McLernon et al., 2016*). The worsening prognosis is related to a decline in oocyte quality with ageing, related to an increasing incidence of chromosomal abnormalities (i.e. an increased risk of aneuploidy) (*Demko et al., 2016; Franasiak et al., 2014; Hale et al., 2014; Shi and Murphy, 2017; te Velde and Pearson, 2002*). These abnormalities decrease the ability of oocytes to be fertilized, as well as their cleavage potential (*Demko et al., 2016; Franasiak et al., 2014; Hale et al., 2014; Shi and Murphy, 2017; te Velde and Pearson, 2002*). Overall, the decrease in oocyte quality has a much greater impact on fertility than declining ovarian reserve. Recently, the POSEIDON group suggested that patients should be classified according to categories related to ART prognosis rather than ovarian reserve and ovarian response (*Alviggi et al., 2016; Humaidan et al., 2016*). This approach emphasizes the impact of age

Age, severity of infertility and TTP/B

1. It is crucial that fertility treatment is managed in a timely manner that avoids over- or under-treatment (American Society for Reproductive Medicine, 2014)

2. In all subfertile women <40 years old, an optimal cumulative IVF outcome could be obtained by performing up to six single embryo transfers. (Gnoth et al., 2003; Goswami et al., 2013)

3. Patient age does not affect the cumulative live-birth rate in oocyte donation cycles if oocyte donors are aged 18–34 years old. (Garrido et al., 2012)

Procedures that could optimise TTP/B

4. Preimplantation genetic testing for aneuploidies can decrease the aneuploidy rate and shorten time to pregnancy and time to healthy singleton delivery (Ubaldi et al., 2015)

5. Preimplantation genetic testing for aneuploidies with comprehensive chromosomal screening can increase both clinical and sustained implantation rates (Dahdouh et al., 2015)

6. In women >35 years old, elective SET combined with enhanced embryo selection using preimplantation genetic testing for aneuploidies can reduce the multiple pregnancy rate while maintaining the cumulative success rate of an IVF program (Ubaldi et al., 2015)

7. A frozen–thawed replacement transfer cycle could be considered immediately after a failed fresh transfer cycle, as this results in a similar clinical pregnancy rate to a frozen–thawed transfer cycle postponed to a later time (Santos-Ribeiro et al., 2016)

8. DuoStim (using FSH and LH in combination with a GnRH antagonist) could be used in patients with reduced ovarian reserve (Ubaldi et al., 2016)

Oocyte retrieval and TTP/B

9. The cumulative live-birth rate (including live births from fresh and frozen–thawed embryos) significantly increases with the number of oocytes retrieved (Drakopoulos et al., 2016)

GnRH antagonists and TTP/B

10. The use of a GnRH antagonist may shorten the treatment period (i.e. fewer stimulation days) with lower FSH consumption and a reduced number of injections (Devroey et al., 2009)

11. In normal responder patients GnRH antagonists have similar efficacy to GnRH agonists (Al-Inany et al., 2016)

12. A GnRH agonist can be used to trigger ovulation in a GnRH antagonist cycle, significantly decreasing the risk of cycle cancellation and ovarian hyperstimulation syndrome in normal responder patients (Al-Inany et al., 2016)

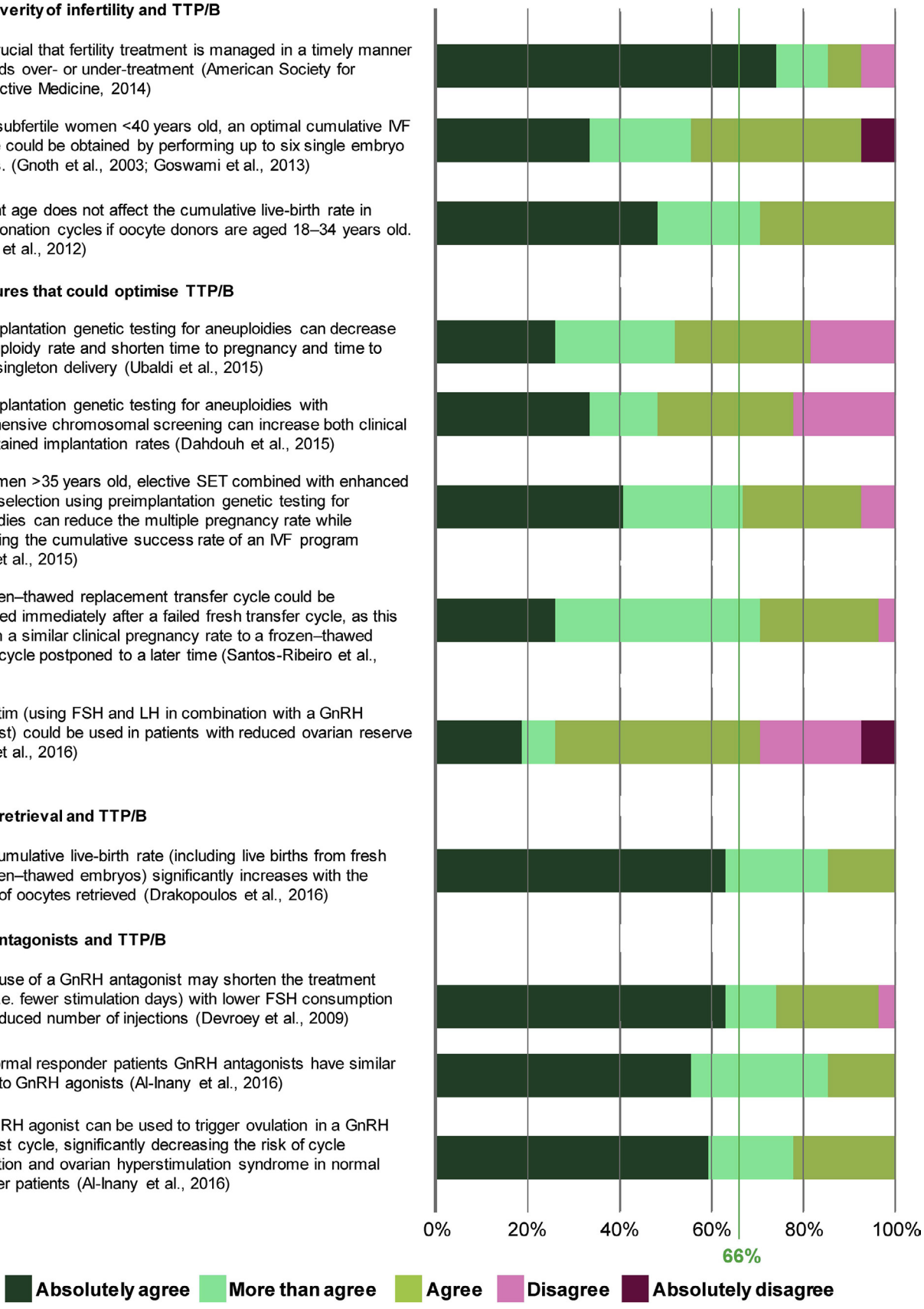

FIGURE 2 Agreement/disagreement with the consensus statements. Results of the participants' agreement with the 12 statements, divided into four categories, using a five-item Likert scale. Consensus was defined as >66% participants agreeing (responding 3, 4 or 5) or disagreeing (responding 1 or 2) with a statement (green line). Consensus was reached on all statements (agreement) after the first round of voting. GnRH = gonadotrophin-releasing hormone; PGS = preimplantation genetic screening; TTP/B = time to pregnancy and time to healthy singleton delivery; SET = single-embryo transfer.

and aneuploidy rates on the success of ovarian stimulation and ART.

Age is the most relevant factor when treating patients, and it is important to ensure that delays due to under-treatment and/or under-diagnosis are avoided. Patients and physicians should be informed about how age affects the urgency for referral to treatment with ART, as well as the appropriate level of treatment. For example, a more targeted and technology-supported approach to treatment may be appropriate in older women, in particular when more than one child is desired. In addition, age, together with other factors affecting fertility, should be taken into account during counselling, including the extent to which management of these risk factors might modify the window available for conception.

2. In all subfertile women <40 years old, an optimal cumulative IVF outcome could be obtained by performing up to six single-embryo transfers (*Gnoth et al., 2003*;*Goswami et al., 2013*)

In premenopausal women, cumulative live birth rate increases with the number of embryo transfer cycles performed (*Gnoth et al., 2003; Smith et al., 2015*). However, the incremental increase in the cumulative live birth rate diminishes with each additional cycle (*Gnoth et al., 2003; Smith et al., 2015*). Published data therefore suggest that at least three embryo transfer cycles (fresh or frozen–thawed) should be performed to ensure that there is at least a 50% cumulative live birth rate (*Goswami et al., 2013; Smith et al., 2015*). These data further suggest that a maximum of six embryo transfer cycles (fresh or frozen–thawed) should be performed (*Goswami et al., 2013; Luke et al., 2012*), as the increase in cumulative live birth rate diminishes after this point and the risks of further transfers outweigh any benefits. However, it should be noted that these references use older data, and are unlikely to reflect more recent advances in clinical practice, including single-embryo transfer (SET) and the use of preimplantation genetic testing (*Gnoth et al., 2003; Goswami et al., 2013; Luke et al., 2012; Smith et al., 2015*). Higher live birth rates would be anticipated if these newer techniques were used, and this could potentially reduce the number of cycles required. Therefore, any decision on a maximum number of embryo transfers to be performed should be based on individual clinical practice data.

The cost-effectiveness of multiple embryo transfer cycles was discussed by the *ESHRE Capri Workshop Group (2015)*. It stated that it is difficult to base ART-related decisions on quality-adjusted life years, as is done for other indications, because more than one person is impacted by the treatment. Instead it suggests that reimbursing IVF treatment involving SET is cost-effective from a macroeconomic standpoint, owing to the average amount of tax generated throughout a person's lifetime (€177,148–800,000) being greater than the anticipated cost of multiple IVF cycles (€20,000 for four cycles).

3. Patient age does not affect the cumulative live birth rate in oocyte donation cycles if oocyte donors are aged 18–34 years old (*Garrido et al., 2012*)

As previously discussed, the age-related decline in fertility observed in premenopausal women is mostly related to declining oocyte quality rather than an effect from hormones or uterine receptivity. Therefore, if donor oocytes from younger women (aged 18–34 years) are used, patient age does not negatively impact the cumulative live birth rate in women with a healthy uterus; similar cumulative live birth rates are observed for women aged <35 years old and those aged ≥40 years (*Garrido et al., 2012*).

Procedures that might optimize time to healthy singleton delivery

4. Preimplantation genetic testing for aneuploidies can decrease the aneuploidy rate and shorten time to pregnancy and time to healthy singleton delivery (*Ubaldi et al., 2015*)

Increased pregnancy and decreased miscarriage rates per transfer have been observed for embryo transfer cycles using preimplantation genetic testing for aneuploidies (PGT-A) compared with cycles using untested embryos (*Coates et al., 2017; Ubaldi et al., 2015*). In one study, which included women with a mean age of 39.5 years, the miscarriage rate per clinical pregnancy was 9.1% when PGT-A was used and 30.3% when it was not; the resulting live birth rate per transferred embryo was 45.0% with PGT-A compared with 10.5% without (*Ubaldi et al., 2015*). The decreased miscarriage rate observed in cycles including PGT-A can be explained by fewer aneuploid embryos being transferred. Owing to the declining oocyte quality observed with increasing age, the magnitude of the difference in pregnancy rate per transfer between untested and PGT-A cycles would be expected to increase with female age. However, it must be noted that the use of PGT-A does not change the per-retrieval pregnancy rate, nor does it increase the total number of live births (*Lee et al., 2015; Rubio et al., 2017*); rather, it enables the more viable embryos to be transferred earlier, and avoids the transfer of embryos with sub-optimal viability.

By reducing the risk of miscarriage, and potentially decreasing the number of transfer cycles required, PGT-A can be expected to decrease the time to pregnancy and time to healthy singleton delivery. A recent randomized controlled trial (RCT) by *Franasiak et al. (2017)* investigated time to pregnancy and live birth in 128 poor ovarian responders randomized to either receive PGT-A or no PGT-A. In this study PGT-A was observed to significantly decrease time to live birth (average decrease of 3 months). Furthermore, an RCT by *Rubio et al., (2017)* demonstrated that PGT-A reduced the time to pregnancy (7.7 versus 14.9 weeks with and without PGT-A, respectively) and decreased the miscarriage rate (2.7% versus 39.0% with and without PGT-A, respectively). Low responder patients might benefit the most from PGT-A because they will have fewer negative outcomes and this may reduce time to pregnancy in patients with reduced available reproductive time. Furthermore, PGT-A may also reduce the psychological impact and emotional strain of failed embryo transfer cycles, which could improve outcomes further because the emotional strain can cause patients to discontinue ART treatment. In addition, the use of PGT-A may potentially reduce the likelihood of futile treatment for recurrent implantation failure (e.g. intravenous immunoglobulin, lipiodol and low-molecular-weight heparin) (*Rubio et al., 2017*).

However, PGT-A has a number of shortcomings, including a 1–5% misdiagnosis rate, a <2–3% embryo non-survival rate following thawing and a lack of consensus on how to deal

with mosaic embryos (*Brezina et al., 2016; Greco et al., 2015; Orvieto and Gleicher, 2016; Scott and Galliano, 2016*). Furthermore, PGT-A is not proven to benefit patients with unexplained recurrent pregnancy loss (*Murugappan et al., 2016*), or patients aged >35 or patients with recurrent implantation failure. There is therefore an urgent need for RCT investigating the effectiveness of PGT-A to be performed in subgroups of patients, including women at advanced maternal age (>35 years) and in women with recurrent implantation failure. These limitations highlight the need to individualize treatment and only offer PGT-A to women with expected poor oocyte quality, as otherwise there may be no benefit and worse outcomes may be obtained (*Gleicher and Orvieto, 2017; Orvieto and Gleicher, 2016*). It is recommended that these studies include time to healthy singleton delivery and cumulative live birth rate as outcome measures.

5. Preimplantation genetic testing for aneuploidies with comprehensive chromosomal screening can increase both clinical and sustained implantation rates (*Dahdouh et al., 2015*)

Increased clinical (risk ratio [RR; 95% confidence interval (CI)]: 1.29 [1.15–1.45]) and sustained implantation rates (RR [95% CI]: 1.39 [1.21–1.60]) have been observed for cycles that included PGT-A with comprehensive chromosomal screening compared with those where it was not included (*Dahdouh et al., 2015; Lee et al., 2015*). These increases were both statistically and clinically significant. As mentioned for the previous statement, this decreased risk of miscarriage could reduce the time to healthy singleton delivery; however, it does not increase the pregnancy rate per cycle or the overall pregnancy rate (*Lee et al., 2015; Rubio et al., 2017*).

6. In women >35 years old, elective SET combined with enhanced embryo selection using preimplantation genetic testing for aneuploidies can reduce the multiple pregnancy rate while maintaining the cumulative success rate of an IVF programme (*Ubaldi et al., 2015*)

The beneficial effects of PGT-A, including the reduced risk for miscarriage, have been discussed previously. Elective SET is recommended to reduce the risk of multiple births, and it is therefore reassuring that when elective SET is used in combination with PGT-A, the cumulative live birth rate is maintained, despite a significant decrease in the multiple pregnancy rate (*Ubaldi et al., 2015*). As the aim of ART treatment is a healthy singleton delivery, the authors suggest that the combination of SET with PGT-A could be an optimal protocol.

7. A frozen–thawed replacement transfer cycle could be considered immediately after a failed fresh transfer cycle, as this results in a similar clinical pregnancy rate to a frozen–thawed transfer cycle postponed to a later time (*Santos-Ribeiro et al., 2016*)

A concern that still persists is that the gonadotrophins used for controlled ovarian stimulation might have a carryover effect that could negatively affect the outcome of subsequent treatment (*Santos-Ribeiro et al., 2016*). This concern may influence decisions concerning the timing of a frozen–thawed embryo transfer cycle after a failed fresh cycle.

However, a retrospective cohort study of 1183 first frozen–thawed embryo transfer cycles reported similar live birth outcomes between patients who underwent transfer ≤22 days after oocyte retrieval (live birth rate 24.5%) and those who underwent frozen–thawed embryo transfer >22 days after oocyte retrieval (live birth rate 24.1%) (*Santos-Ribeiro et al., 2016*). More patients (n = 986) had embryo transfer after >22 days but the time since the end of the preceding IVF cycle was not specified. Performing frozen–thawed embryo transfers without a delay period will contribute to reducing the time to a healthy single delivery by eliminating unnecessary delays between cycles. In addition, the removal of an enforced delay period will provide patients with greater flexibility and the transfer can be conducted according to each individual patient's schedule. This may also help reduce the psychological burden associated with the various waiting periods inherent during ART treatment.

Although clinically a very relevant issue, there is currently a paucity of data on this topic, with the only available data coming from a retrospective cohort study (*Santos-Ribeiro et al., 2016*). RCTs investigating outcomes following frozen–thawed embryo transfers conducted either with or without a delay should therefore be conducted. These RCTs should also consider the physiological burden related to any delays using objective measurement tools.

8. DuoStim (using FSH and LH in combination with a GnRH antagonist) could be used in patients with reduced ovarian reserve (*Ubaldi et al., 2016*)

A small clinical study that included 43 patients with poor ovarian reserve demonstrated that an increased yield of oocytes can be obtained from low responders by performing back-to-back stimulations, one beginning at the onset of menses (the traditional start time) and one at the onset of the luteal phase of the same cycle (5 days after the first oocyte retrieval) (*Ubaldi et al., 2016*). After each stimulation, when at least two follicles had reached 17–18 mm in diameter, ovulation was triggered with a single subcutaneous bolus of 0.5 ml buserelin and oocyte retrieval was performed after 35 h via transvaginal ultrasound-guided aspiration. In this study, both stimulations resulted in similar numbers of metaphase II (MII) oocytes and pregnancy outcomes were similar in patients regardless of the stimulation phase in which the transferred embryos were produced (*Ubaldi et al., 2016*). This approach has also been referred to in the literature as the Shanghai protocol (*Kuang et al., 2014*).

It is important to note that although from a physiological point of view this approach could be used for all patients, we recommend that it should only be used when the need to obtain oocytes is urgent, including patients with malignant diseases undergoing oocyte cryopreservation and patients of advanced maternal age or with reduced ovarian reserve. One participant of the Delphi consensus absolutely disagreed with this approach, owing to the low level of evidence available. However, the majority of the participants agreed that this approach appeared to offer advantages relating to the potentially increased number of oocytes retrieved over a short period of time. Owing to the limited evidence available at present, further studies should be devoted to this approach with a particular focus on optimizing the protocols used before it is recommended for use in routine

clinical practice. These studies should address questions including whether GnRH antagonist use is required for the luteal phase stimulation, and if recombinant FSH should be used alone or in combination with luteinizing hormone (LH), and whether these choices affect the duration of stimulation and the gonadotrophin doses required.

Oocyte retrieval and time to healthy singleton delivery

9. The cumulative live birth rate (including live births from fresh and frozen–thawed embryos) significantly increases with the number of oocytes retrieved (*Drakopoulos et al., 2016*)

The number of oocytes retrieved during controlled ovarian stimulation is strongly correlated with treatment outcomes, including the likelihood of live birth, both per cycle and per patient (*Drakopoulos et al., 2016; McLernon et al., 2016; Steward et al., 2014; Sunkara et al., 2011*). The cumulative live birth rate (including both fresh and frozen–thawed embryo transfers) improves as the number of retrieved oocytes increases, with poor ovarian responders (1–3 oocytes retrieved) having the worst outcomes (*Drakopoulos et al., 2016*). Over a single fresh-embryo transfer cycle, the live birth rate is similar for all patients with >3 oocytes retrieved; however, when subsequent frozen–thawed embryo transfers are also considered, clear differences in cumulative live birth rate are observed with increasing number of oocytes retrieved (cumulative live birth rate: 21.7% in patients with 1–3 oocytes retrieved; 39.7% with 4–9 retrieved; 50.5% with 10–15 retrieved; and 61.5% with >15 oocytes retrieved) (*Drakopoulos et al., 2016*). In addition, there appears to be no impairment in the quality of oocytes retrieved from high responders. The aim of controlled ovarian stimulation should therefore be to obtain the maximum number of oocytes possible (*Briggs et al., 2015; Drakopoulos et al., 2016*).

The improvement in outcomes observed when a greater number of oocytes are retrieved is related to the higher odds that at least one high-quality embryo will be available. Should several high-quality embryos be available, some can be frozen for use in later rounds of embryo transfer. However, the optimal target number of oocytes for retrieval should be individualized according to patient age, any underlying pathology that might affect controlled ovarian stimulation (e.g. polycystic ovary syndrome) in relationship to ovarian reserve and ovarian response, and the desired number of children.

GnRH antagonist use and time to healthy singleton delivery

10. The use of a GnRH antagonist may shorten the treatment period (i.e. fewer stimulation days) with lower FSH consumption and a reduced number of injections (*Devroey et al., 2009*)

Controlled ovarian stimulation protocols generally include the use of either a GnRH agonist or a GnRH antagonist to prevent a premature rise in LH, enabling the collection of oocytes (*Depalo et al., 2012; Devroey et al., 2009; Khalaf and Sunkara, 2015; Reichman and Rosenwaks, 2014; Tarlatzis et al., 2006*). However, use of GnRH antagonists is proposed to have a number of advantages compared with the use of GnRH agonists, including the lack of a gonadotrophin flare and a reduction in the length of treatment required, as well as a reduction in the amount of gonadotrophin required for controlled ovarian stimulation (*Depalo et al., 2012; Devroey et al., 2009; Khalaf and Sunkara, 2015; Reichman and Rosenwaks, 2014; Tarlatzis et al., 2006*).

A recent *post hoc* analysis of a Phase IV, dual-centre, open-label RCT, including 1050 women allocated (1:1) to a short GnRH antagonist or a long GnRH agonist protocol, reported similar cumulative live birth rates in patients who received a GnRH antagonist protocol and those who received a GnRH agonist protocol (34.1% versus 31.2%, respectively) (*Toftager et al., 2017*). However, a shorter mean time to first live birth was also observed with a GnRH antagonist protocol compared with a GnRH agonist protocol (11.0 versus 11.5 months, respectively; $P < 0.01$). The use of GnRH antagonists may, therefore, contribute to reducing the time to healthy singleton delivery.

Further studies are needed to compare all different drug protocols (agonist versus antagonist) in order to evaluate the impact of these treatment choices on the time interval between ART cycles and on time to healthy singleton delivery. In addition, studies are needed to investigate the impact of gonadotrophin choice on the real time between cycles, the cost of treatment and whether premedication has an impact on the synchronization of follicular cohort.

11. In normal responder patients GnRH antagonists have similar efficacy to GnRH agonists (*Al-Inany et al., 2016*)

A meta-analysis of 12 RCT, including 2302 patients, demonstrated that GnRH antagonists and long-course GnRH agonists have a similar efficacy profile related to live birth, when used for controlled ovarian stimulation in normal responder patients (odds ratio [OR; 95% CI]: 1.02 [0.85, 1.23]) (*Al-Inany et al., 2016*). This was also observed in meta-analyses which evaluated live birth rates in four RCTs, including 753 patients (*Xiao et al., 2014*) and 10 RCTs, including 2590 patients (*Lambalk et al., 2017*). There is less evidence for other groups of patients; no difference in live birth rates with an antagonist or an agonist protocol was suggested by a meta-analysis of three RCT including 544 poor ovarian responders and a meta-analysis of three RCT including 363 patients with PCOS (*Lambalk et al., 2017*). Therefore, this area requires further study to improve individualized ovarian stimulation protocols.

12. A GnRH agonist can be used to trigger ovulation in a GnRH antagonist cycle, significantly decreasing the risk of cycle cancellation and ovarian hyperstimulation syndrome in normal responder patients (*Al-Inany et al., 2016*)

A meta-analysis of 36 RCTs, including 7944 patients, demonstrated that GnRH antagonist use was associated with a lower incidence of any grade of ovarian hyperstimulation syndrome (OHSS) than GnRH agonist use (OR [95% CI]: 0.61 [0.51, 0.72]) (*Al-Inany et al., 2016*). GnRH antagonist use was also observed to be associated with a lower incidence of cycle cancellation due to high risk of OHSS than GnRH agonist use (OR [95% CI]: 0.47 [0.32, 0.69]; data from 19 RCT including 4256 patients) (*Al-Inany et al., 2016*). Cycle cancellation due to poor ovarian response was higher with GnRH antagonist use than with GnRH agonist use (OR [95% CI]: 1.32 [1.06, 1.65]; data from 25 RCT including 5230 patients). The reduced risk for OHSS observed with GnRH antagonist use results from the use of a single bolus of GnRH agonist to trigger final oocyte maturation in patients at risk of OHSS, which is not possible when a GnRH agonist protocol is used.

DISCUSSION

The most important message that emerged from this consensus on time to healthy singleton delivery was the importance of timely, individualized care of the infertile patient, in particular for women aged >35 years, as time is a significant negative issue relating to fertility. One of the main impediments to timely treatment is delay when referring patients for fertility treatment. Therefore, both primary care physicians and the general public should be educated on the impact of age on fertility, ensuring patients are referred for specialist care in a timely manner. Time to pregnancy and time to healthy singleton delivery should be fully integrated into this education and should be embedded in all treatment decisions, with the goal of streamlining the diagnosis of infertility, reducing inappropriate 'relax and it will happen' counselling and encouraging rapid referral. Education of the public should help reduce the idea that primary care physicians are making hasty decisions when referring for specialist fertility care. One way to emphasize the impact of age on fertility would be to include the curve of IVF success rate according to age on patient hand-outs. This would also ensure that patients are fully informed when making any shared treatment decisions. In addition, patients should be counselled on the specific number of oocytes needed to obtain one euploid blastocyst. One way to speed up referral might be to alter guidance to shorten the time to referral to specialist infertility care to 6 months for all patients, as this may avoid confusion about which patients should have more rapid referral.

Any discussion about fertility should include goals relating to desired family size, because the desire for more children will reduce the time available for each pregnancy. The importance of desired family size was demonstrated by an established computer-simulation model of fertility, which was used to assess the chances of realizing a one-, two- or three-child family (*Habbema et al., 2015*). This model suggests that in order to have a ≥90% chance of achieving a one-, two- or three-child family, couples should start trying to conceive when the female partner is ≤35, ≤31 and ≤28 years, respectively, if IVF is an acceptable option. If IVF is not acceptable, couples should start no later than 32, 27 and 23 years if they desire a one-, two- or three-child family, respectively. There are also a number of models available that can provide an estimated live birth rate for women with infertility, including the Templeton, Nelson and McLernon models (*McLernon et al., 2016; Nelson and Lawlor, 2011; Templeton et al., 1996*). These should be used to predict a patient's prognosis but may require fitting to each centre's data (*Arvis et al., 2012*). Another approach suggested by the POSEIDON group is to categorize patients according to their prognosis, emphasizing how age and aneuploidy rate are important factors in the success of ovarian stimulation and ART (*Alviggi et al., 2016*).

Once a patient has been referred for fertility treatment it is important that optimized, streamlined protocols are used, which are both data-driven and data-targeted. For example, as discussed in the Introduction, simple changes to the approach taken to ART treatment can reduce the time taken for three IVF cycles from approximately 2 years to 0.5 years. The FASST trial, which compared the time to pregnancy, live birth rate and cost-effectiveness of a standard treatment pathway (three cycles of clomiphene citrate/intrauterine insemination [IUI], followed by three cycles of FSH/IUI, followed by up to six cycles of IVF) with an accelerated treatment pathway (three cycles of clomiphene citrate/IUI, followed by up to six cycles of IVF) also demonstrates this (*Reindollar et al., 2010*). The accelerated pathway was associated with an increased rate of pregnancy, a shorter median time to pregnancy and greater cost-effectiveness compared with the standard pathway. This demonstrates that streamlining and optimizing treatment pathways can significantly improve outcomes. Optimized protocols should also aim to reduce the risk for negative outcomes, including OHSS and early pregnancy loss, and also the number of procedures conducted, which should, overall, reduce the time to healthy singleton delivery.

The aim of controlled ovarian stimulation should be to obtain the highest possible number of oocytes, while avoiding extreme and potentially dangerous responses, as this increases the probability of a successful live birth. Owing to the reduced risk of OHSS, it is recommended that a GnRH antagonist protocol, with a GnRH agonist to trigger final follicular maturation, is used. The use of a GnRH antagonist protocol can also reduce the duration of stimulation required, with fewer injections and lower overall FSH consumption, without reducing the reproductive outcome. This should also reduce the cost of treatment because less drug is required.

It is important that good-quality embryos are transferred, to reduce the risk of miscarriage. PGT-A in combination with SET is therefore recommended in certain patient groups, as the use of PGT-A avoids the transfer of aneuploid embryos. This is of increasing importance when treating older women as oocyte quality decreases with age. In the authors' experience, patients are generally more than willing to consent to PGT-A, even if this runs the risk of no transfer owing to the exclusion of all embryos. The short-term expenses related to PGT-A must be balanced in each case against the costs of miscarriages and failed cycles. These economic considerations should be kept in mind when counselling patients about treatment options.

Once embryos are available for transfer, published data suggest that a maximum of six SET (fresh or frozen–thawed) should be performed. However, owing to the high probability of variability in practice between clinics and also between physicians within the same clinic, a lower maximum may be appropriate and any decision about the maximum number of embryo transfers to be performed should be made based on clinical practice data.

Despite the importance of time to healthy singleton delivery as a consideration for deciding appropriate ART strategies, only a few studies have investigated the overall duration of treatment required to achieve this outcome. More research is therefore necessary, in particular on the impact of treatment choice on time to pregnancy. The most pressing need is to evaluate the duration between a patient's perception of a fertility problem and the initiation of fertility treatment. This could then help drive discussion of timely referral. Studies that evaluate the time between cycles with all of the currently available drug protocols in all patient subsets are also needed.

Time to healthy singleton delivery should be considered as an outcome

for new clinical trials investigating ART treatments. The outcome of these studies would aid clinicians when counselling patients and assist in treatment selection for patients who have a poorer prognosis owing to a shorter timeframe within which ART treatment is more likely to be successful. Furthermore, this might allow analytics to be performed to understand what optimal stimulation would look like for each individual patient and to develop treatment algorithms. There is also a lack of well-designed cost–benefit studies, in which the costs of specific approaches on the one hand, and the estimated cost of each treatment failure, miscarriage and unit of time until live birth on the other, are considered.

This consensus has a number of limitations. Firstly, it represents only the collective opinion of the experts who participated in this Delphi consensus and does not represent an exhaustive list of statements on time to healthy singleton delivery, nor does it represent the outcomes of any new systematic review of the literature or meta-analysis. The experts were mainly from Europe and the USA and their views may not represent those held by experts in other areas of the world (including Asia, Africa and Australia). As in all research of this type, there is the possibility that the experts who agreed to participate would be those with particularly strong opinions, leading to selection bias. Furthermore, not all statements reached 100% agreement, with some statements reaching consensus even though a minority of participants absolutely disagreed with them. Finally, the statements represent the point of view of healthcare professional experts, and patients should be consulted on which statements they consider provide minimal burden of treatment for optimum output.

In conclusion, because the mean age of women seeking ART treatment is increasing, time to healthy singleton delivery is becoming a more important factor when deciding appropriate ART strategies. Greater efforts are needed to educate family physicians/general practitioners about age-related fertility decline. This physician education should ensure that women are referred before age-related fertility decline overly reduces the chances of successful treatment. Public awareness of the age-related decline in fertility also needs to be increased, ensuring patients approach their physician with any concerns about their fertility in a timely manner. Finally, the relevance of time in making decisions related to infertility treatment should be included in patient counselling.

Once a patient is referred, a patient-centric approach to infertility treatment is essential, taking into account the patient's point of view and priorities when discussing treatment options. This approach should include discussion of what completion of treatment means to the patient, as this might further influence the importance of time; for example, if a patient desires more than one child, time might be more important.

ACKNOWLEDGEMENTS

In addition to the authors, the Delphi TTP Consensus Group included: Brian M Berger, Francisco Arredondo, Catherine Avril, Pedro Barri, Jose Bellver, Christophe Blockeel, Andrea Borini, Amber Cooper, Didier Dewailly, Rui Ferriani, Alfredo Guillen, Semra Kahraman, Joaquín Llacer, Anja Bisgaard Pinborg, Paolo Levi Setti, Bülent Urman. Sanitanova Srl supported the Delphi consensus by identifying participants for Step 1, providing logistical support for meetings and writing a report summarizing outcomes.
Medical writing support was provided by Alexander Jones, inScience Communications, and was funded by Merck KGaA, Darmstadt, Germany. Alexander Jones did not participate in the Delphi consensus development process. This Delphi consensus was funded by Merck KGaA and coordinated by Sanitanova Srl.

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Received 17 January 2018; received in revised form 26 September 2018; accepted 27 September 2018.