Chapter 1
Introduction: The Scope of the Problem with Diminished Ovarian Reserve

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1.1 Definitions: Fertility, Fecundability, and Fecundity

Per the American Society for Reproductive Medicine (ASRM), fertility is defined as the capacity to produce a child [1]. Fecundability is defined as the probability of pregnancy per month. Strict definition of fecundability is the probability of conceiving in a given ovulatory menstrual cycle. Fecundity, on the other hand, is the probability to have a live birth within a single menstrual cycle. Monthly fecundability is highest during the first 3 months of trying, and about 80% of the couples achieve pregnancy within the first 6 months of trying. Again, per ASRM, infertility is defined as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse or sperm exposure. However an earlier evaluation for possible treatment after 6 months without conception for women over age 35 years is recommended [2]. This recommendation is because fertility declines with female aging. Monthly fecundability rates decline by close to 50% between the ages of 35 and 39 years as compared to the same rates noted between the ages of 19 and 26 years [1].

1.2 Female Age

The classic data on the rate of natural pregnancy per female age graph shows that the natural conception rates decline from early to mid-30s and steeper decline is expected after 40 years of age (Fig. 1.1). Not surprisingly, in the United States, the

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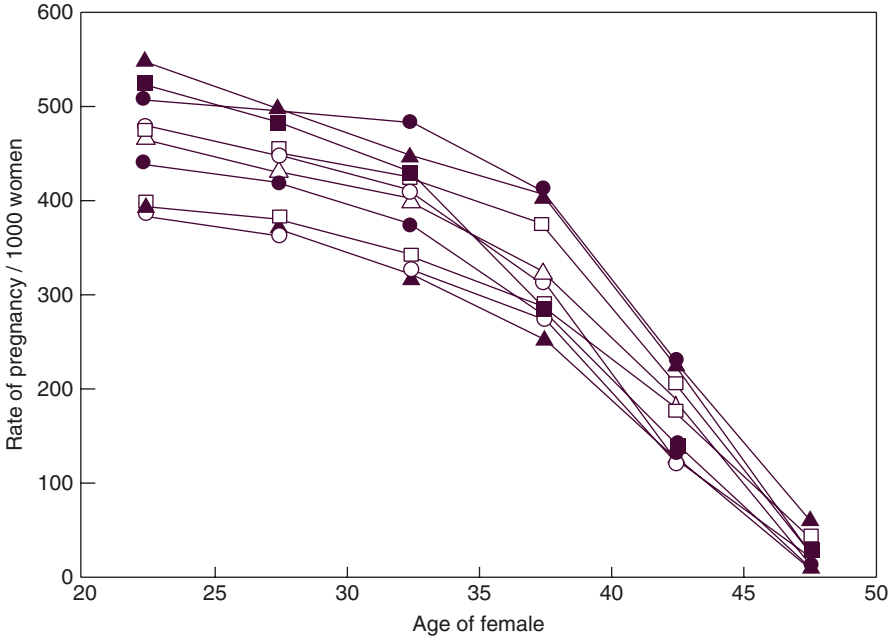

Fig. 1.1 Pregnancy rate per 1000 women in different populations from 1700 to 1950, with permission [1]

Society for Assisted Reproductive Technology's (SART) annual assisted reproductive technology treatment outcome report clearly shows that pregnancy and live birth rates decline with advancing female age (Fig. 1.2) https://www.cdc.gov/art/pdf/2015-national-summary-slides/ART_2015_graphs_and_charts.pdf. Female age is in fact the most important determinant of live birth with in vitro fertilization (IVF) treatment. This data also suggests that decline in live birth rates with treatment starts in the early 30s; then this decline becomes more pronounced after the mid-30s; and steeper decline is seen at and after age of 40.

The fertility trends at least in OECD (Organisation for Economic Co-operation and Development) countries suggest that the age of first birth in women is increasing around the globe. The average mean age of women at first birth has risen by almost 3 years in the last two decades in OECD countries (Fig. 1.3). In the United States, while birth rate decline is observed in teenage girls and in women between 20–29 and 30–34 years of age, birth rate increase is noted within the age groups of 35–39 and 40–44 years old. Therefore, females are postponing their pregnancies until later years of the reproductive period.

OECD (2016), "The average mean age of women at first birth has risen by almost three years in the last two decades: Mean age of women at first birth, 1995 and 2014 (or nearest year)," in *General context indicators*, OECD Publishing, Paris, https://doi.org/10.1787/soc_glance-2016-graph37-en.

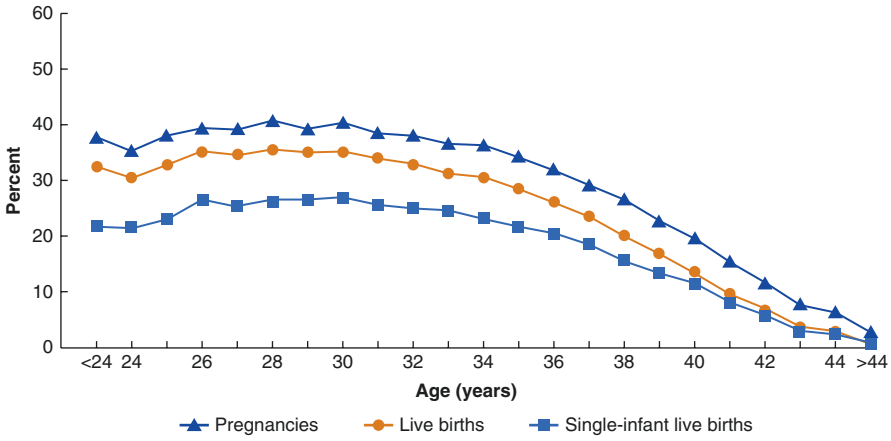

Fig. 1.2 SART 2015 Assisted Reproductive Technology (ART) summary report: percentage of pregnancies, live births, and single-infant live births by age of woman as a result of ART treatment (https://www.cdc.gov/art/pdf/2015-national-summary-slides/ART_2015_graphs_and_charts.pdf)

The most important reflection of delayed child-bearing in females is fertility decline as expected by advancing age. This fertility decline is associated with diminished ovarian reserve and diminished oocyte/embryo quality with aging. Diminished ovarian reserve itself may also be noted at any age when the women present with infertility. Although female fertility decreases with aging, the pace of reproductive decline can be different in each woman [3].

1.3 Paradigm of Diminished Ovarian Reserve as a Clinical Reflection of Poor Ovarian Response in Assisted Reproductive Technology

Diminished ovarian reserve (DOR) is one of the recent challenges clinicians and patients alike face in fertility treatment. Since the controlled ovarian stimulations became a norm in assisted reproductive technology (ART) cycles, it has been realized that some women just do not respond well to ovarian stimulation, while others suffer from ovarian hyperstimulation syndrome (OHSS). Therefore, the terms "poor responder" and "high responder" have been used, respectively.

There are various definitions of these terms but we can first review various definitions of DOR. National ART Surveillance System guideline defines DOR as "reduced fecundity related to diminished ovarian function; includes high FSH or high estradiol measured in the early follicular phase or during a clomiphene citrate challenge test; reduced ovarian volume related to congenital, medical, surgical or other causes; or advanced maternal age (>40)" [4].

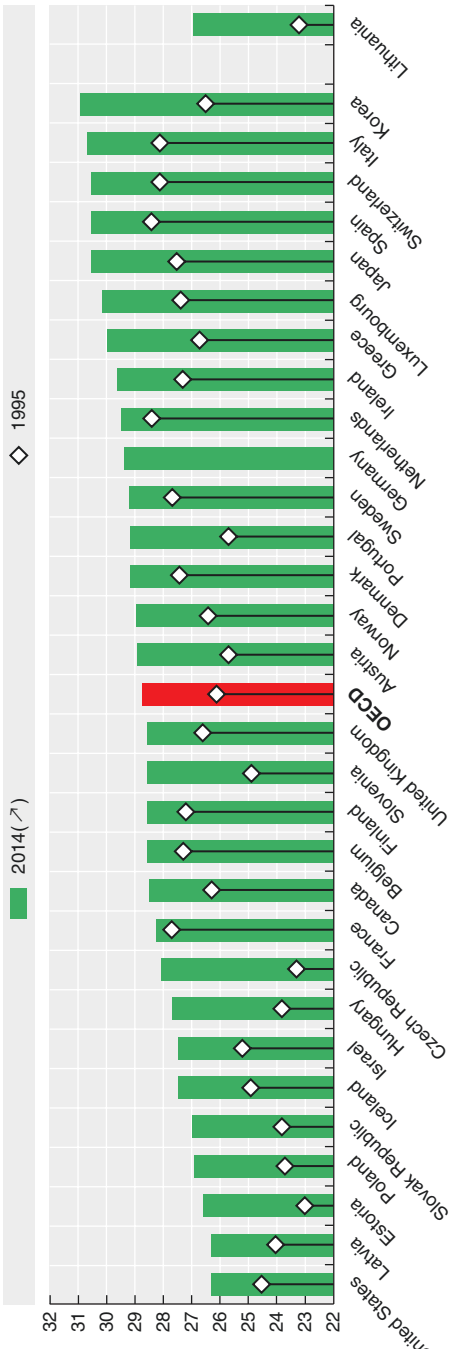

Fig. 1.3 The mean age of women at first birth has risen by almost 3 years in the last two decades

Definition of assisted reproductive technology per Office of the Federal Register (USA) is as follows: "*Assisted reproductive technology (ART)*—All treatments or procedures that include the handling of human oocytes or embryos for the purpose of establishing a pregnancy. This includes, but is not limited to in vitro fertilization and transcervical embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, oocyte or embryo cryopreservation, oocyte or embryo donation, and gestational surrogacy. ART does not include assisted insemination using sperm from either a woman's partner or sperm donor." [5]

In the same federal registry document, DOR was defined as a condition of reduced fecundity related to diminished ovarian function based on clinical assessment; often indicated by FSH ≥ 10 mIU/ mL or AMH < 1 ng/mL (https://www.gpo.gov/fdsys/pkg/FR-2015-08-26/pdf/2015-21108.pdf).

In the National ART Registry of the United States, in 2005 the DOR diagnosis is present in an average of 8.2% of ART cycles, while 39.9% of ART cycles were performed in women younger than 35 years of age. In 2015, the same registry shows that 31% of the ART cycles has the DOR diagnosis, while 38.1% of the ART cycles were from women <35 years of age. DOR diagnosis can be as high as 69% [6]. Therefore, DOR diagnosis is much more frequently made, while the proportion of women at or ≥35 years of age undergoing ART has increased by close to 2%. This discrepancy may be due to the more widespread use of ovarian reserve assessment before ART. In addition, more couples may be visiting fertility centers for infertility associated with DOR, and DOR may be becoming a more frequent indication for ART.

1.3.1 Poor Ovarian Response per European Society of Human Reproduction and Embryology

The European Society of Human Reproduction and Embryology (ESHRE) came up with a consensus definition for poor ovarian response (POR) for in vitro fertilization [7]. The Bologna criteria for POR is shown in Table 1.1. Many studies on POR used differing criteria and reported variable conclusions whether

Table 1.1 The "Bologna criteria" for poor ovarian response (POR): two out of three should be present[a]

1. Advanced maternal age ≥ 40 years or any other risk factor for POR
2. A previous POR defined as ≤3 oocytes with conventional ovarian stimulation
3. An abnormal ovarian reserve test: AFC < 5–7 or AMH < 0.5–1.1 ng/mL

AFC antral follicle count, AMH anti-Mullerian hormone

[a]Two previous cycles with POR after maximal stimulation are sufficient to define POR in the absence of advanced maternal age and abnormal ovarian reserve test

any particular IVF stimulation protocol results in better IVF outcomes [8]. The rationale was if there is a unified definition for POR, future research could be performed on such patient populations to come up with a unified global IVF treatment protocol for such patients. Shortly after its implementation, the criticisms followed since once again, one unified paradigm did not fit all. Although the majority of the POR may be due to DOR, some POR cases just cannot be explained with Bologna criteria. In addition, POR definition heavily relies on conventional IVF stimulation protocols, which mostly focus on retrieving as much oocytes as possible after a treatment cycle, since in such protocols it is believed that the number of oocytes retrieved is the most important treatment outcome parameter to predict clinical pregnancy and live birth. The Bologna criteria actually indirectly supports high-dose IVF stimulation protocols as the legitimate treatment approaches for such patients by mentioning about poorly defined "maximal stimulation" (Table 1.1).

Various endocrine and ultrasound markers and even some dynamic tests have been utilized to predict POR. Accordingly, POR has been defined by various criteria until the Bologna criteria for POR was recommended through consensus so that such patients could be defined in a unified manner so that the treatments can also be unified in such patients [7].

However, recently these criteria have been the focus of criticism since some patients showing poor response simply do not meet the Bologna criteria. This is in spite of the complaints that there was no accepted definition of POR, and therefore it will always be difficult to compare the results in published studies. In addition, POR may be due to systemic inflammatory diseases, nutritional disorders, advanced stage cancers without presence of the DOR per the age, AMH, and AFC criteria. Then Bologna consensus may not meet the needs. The criteria used for all such definitions relies on the female age equal or above 40 years, the serum markers like anti-Mullerian hormone (AMH) and ultrasound markers like antral follicle count (AFC), the number of oocytes collected in prior treatment cycles, highest estradiol levels achieved, and history of gonadotoxic treatments or ovarian surgery. Still the threshold levels for AFC and AMH vary in the latest Bologna criteria, while measurement of these two parameters is open to subjective and methodological biases, respectively [4, 9].

The AFC assessment of ≥2 mm antral follicles by transvaginal ultrasound as a marker of ovarian aging was first reported in 1996 by a study performed in volunteers aged between 22 and 42 years [10]. The authors noted that antral follicle counts decreased by aging. This measurement later evaluated to be one of the best predictors of ovarian response [11, 12]. Over the years, there were debates about the upper limit of antral follicle size or diameters measured by ultrasound. Diameters between 2 and 10 mm were included in some guidelines like Rotterdam criteria defining polycystic ovary morphology [13]. However, to better assess the controlled ovarian stimulation outcome, different upper thresholds less than 10 mm were proposed. One study reported that the number of

antra follicles 2–6 mm decreased by age, but those between 7 and 10 mm stayed constant [14]. It was demonstrated that AMH expression is strongly observed in secondary, preantral, and small antral follicles up to the diameter of 4–6 mm. The AMH expression then decreases with further follicle growth and disappears in follicles measuring >8 mm in diameters. As expected, AMH expression is not observed in primordial follicles, and it is only weakly expressed in some primary follicles [15]. It was reported that the antral follicles measuring between 2 and 6 mm could be the best predictor for the number of mature oocytes retrieved at oocyte retrieval and was strongly associated with serum AMH levels [9]. Therefore, it is reasonable to focus on antral follicles between 2 and 6 mm while performing AFC.

1.3.2 Poor Ovarian Response Criteria per Prognostic Factors

There is another recent classification of patients with expected POR. The Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) group proposed a classification of POR patients into four groups per age; the presentation of unexpected POR, if previously stimulated, predicted poor prognosis, AFC, and AMH levels [16]. The main reasons for this new stratification effort for POR was due to the fact that Bologna criteria is disregarding female age effects on pregnancy outcomes regardless of the number of oocytes retrieved. The authors intended to change the paradigm from POR to low prognosis concept. Therefore, clinically more relevant criteria were suggested. They brought two new groups for defining low-prognosis patients according to how they responded to a conventional ovarian stimulation for IVF. First one is "suboptimal response" defined as the retrieval of four to nine oocytes, which is associated, at any given age, with a significantly lower live birth rate compared with normal responders defined those with 10–15 oocytes, in which authors supported this definition by quoting a retrospective study [17]. Second one is "hyporesponse" for those needing higher dose of gonadotropins and prolonged stimulation to retrieve more than three oocytes which may be due to genetic issues as authors quoted another study to support this definition [18]. Then the age threshold of 35 years in relevance to expected embryo aneuploidy rate, and AMH and AFC, as the ovarian reserve markers are also included to define groups. This is also a more dynamic assessment since it includes before, during, and after stimulation observations. POSEIDON classification of low-prognosis patients is summarized in Table 1.2.

The authors believe that the low prognosis concept will better help to personalize ART treatment protocols. It may also lead to define those patients with genetic polymorphism related to gonadotropins and their receptors [16].

Table 1.2 POSEIDON group for low prognosis for assisted reproductive technology treatment

Group	Subgroup	Description
1		Age < 35 years with acceptable pre-stimulation ovarian reserve (AFC ≥5, AMH ≥1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response
	1a	Fewer than four oocytes
	1b	Four to nine oocytes after standard ovarian stimulation, who, at any age, have a lower live birth rate than age-matched normal responders
2		Age ≥ 35 years with acceptable pre-stimulation ovarian reserve (AFC ≥5, AMH ≥1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response
	2a	Fewer than four oocytes
	2b	Four to nine oocytes after standard ovarian stimulation, who, at any age, have a lower live birth rate than age-matched normal responders.
3		Age < 35 years with poor ovarian reserve pre-stimulation parameters (AFC <5, AMH <1.2 ng/mL)
4		Age ≥ 35 years with poor ovarian reserve pre-stimulation parameters (AFC <5, AMH <1.2 ng/mL)

Modified from [16]

1.4 Conclusion

Women are postponing their pregnancies due to various reasons as also discussed in ovarian and hypothalamic aging section. The fertility decline is noted in women starting from late 20s to early 30s. This is mostly related to decrease in ovarian reserve, which we define as the quantity decline and decrease in oocyte quality, which we consider as quality decline. Poor ovarian response criteria per ESHRE has been heavily based on quantity decline, while the age criteria which mostly reflects quality, as will be discussed in Chap. 2, is included when the female age is ≥40 years. Although Bologna criteria was proposed to achieve more unified definitions for research, it introduced its own inherent problems due its assumptions, which may not reflect the prognosis. Recently, attempts are made to have more individualized criteria for POR focusing on expected low prognosis by POSEIDON group. Regardless, the diagnoses of DOR in ART cycles are increasing, while most of the women with POR are those with DOR. These women are a heterogeneous group who may require personalized approaches for ART treatments.

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