

# Natural Cycle and Minimal Stimulation IVF

From Physiology to Clinical  
Practice

Michael von Wolff  
*Editor*



Springer

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*This book is dedicated to all those who are willing to leave the trodden path of conventional IVF to offer their patients a broad spectrum of up-to-date, individualized and patient-orientated IVF treatments.*

# Foreword

The first child born following IVF in 1978, Louise Brown, was from an unstimulated cycle. Professor Bob Edwards previous attempts using IVF along with ovarian stimulation using clomiphene citrate failed, which he contributed to the induced luteal phase abnormalities. Subsequent mainstream development of IVF—chiefly in Australia and the USA—led to the belief that ovarian stimulation should be considered an integral part of IVF. In an attempt to overcome shortcomings in the in vitro fertilization laboratory procedures, the general principle became—and by some still is—the more oocytes to start with wasteful laboratory procedures the better.

Hence, extremely complex, costly and hazardous ovarian stimulation regimens have been developed over the last three decades involving multiple drugs and creating the need for frequent hospital visits and intense monitoring of ovarian response. In quite a few programmes, the total cost associated with ovarian stimulation exceeds the expenses of the IVF procedure itself.

Indeed, numerous studies confirmed that IVF cycles starting with a greater number of available oocytes is associated with higher pregnancy rates. This is often erroneously used to justify high dose intense ovarian stimulation protocols. The wisdom that high oocyte numbers following stimulation primarily represent good prognosis patients, no matter what you do, is often ignored.

Current IVF with much improved laboratory performance can certainly be performed in cycles with no ovarian stimulation. This approach renders IVF much faster, cheaper and with less burden of treatment and reduced chances for complications. Overall, pregnancy rates per IVF cycle are certainly reduced which should be viewed in the context of the many advantages. Moreover, cumulative pregnancy rates over a given period of time (involving multiple IVF cycles) may run favourable, especially in good prognosis patients.

Over the years many mild (or minimal) ovarian stimulation protocols have been developed using different compounds and dosing regimens. In addition, multiple studies have now shown comparable pregnancy rates, reduced dropouts, and the association with reduced cost and complications. A more holistic approach on infertility care cannot only focus on “success” of treatment, completely ignoring induced

side effects, chances for complications, and cost rendering IVF treatment out of reach for many throughout the world.

The current book is a well-timed, comprehensive attempt to cover this rapidly developing and now more accepted field of natural cycle and mild (or minimal) stimulation IVF.

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# Preface

The first pregnancies and births after in vitro fertilisation (IVF) occurred in 1978 and 1979 after natural cycle IVF (NC-IVF) [1]. The IVF treatments were led by Robert Geoffrey Edwards, a geneticist who received the Nobel Prize in Physiology and Medicine in 2010 for his contributions to IVF, and Patrick Steptoe, a gynaecologist.

Interestingly, Edwards and Steptoe had already developed IVF therapy with gonadotropin stimulation. As these treatments did not result in pregnancy, they continued their IVF programme with NC-IVF therapies in 1977. As a result, four clinical pregnancies and two births developed, including that of Louise Brown, who was born on 25 July 1978 (see Chap. 4).

These first NC-IVF treatments cannot be compared to the NC-IVF therapies used today. For example, Edwards and Steptoe retrieved an oocyte laparoscopically, and the effectiveness of IVF was much lower at that time. The effectiveness of IVF increased by leaps and bounds after it was recognised that a gonadotropin-induced polyfollicular response led to luteal phase insufficiency. Luteal phase support was introduced, and the chances of IVF success increased significantly due to the large number of oocytes availability.

In recent years, however, it has become apparent that conventional IVF with high-dose gonadotropin stimulation is not the best approach for all couples for the following reasons:

- The proportion of women with a low ovarian reserve increases, in whom only a few oocytes can be obtained despite high-dose gonadotropin stimulation.
- High-dose gonadotropin stimulation can be disadvantageous in patients with a high ovarian reserve as the cumulative live birth rate decreases with a very high number of collected oocytes.
- An increasing proportion of women are critical of hormone therapy because of concerns about side effects.
- The cost per treatment cycle is significantly lower with NC-IVF or minimal stimulation IVF, so some patients might prefer to start with cheaper treatment cycles.



It is also significant that IVF laboratories have made such considerable progress that the chances of success per oocyte have increased to the point where a high success rate is possible even with only one or with a few oocytes. Accordingly, studies now show that the success rate with low-dose gonadotropin stimulation, also called minimal stimulation IVF, or even NC-IVF can be just as effective as conventional IVF therapy with high-dose gonadotropin stimulation. Since NC-IVF or minimal stimulation IVF therapy cycles can be performed monthly, the success rate per therapy time may even be higher in some patients.

Accordingly, NC-IVF or minimal stimulation IVF therapies are becoming increasingly widespread. The spread is currently still hampered by the reimbursement of IVF therapies, which is no longer up to date in most countries. In most cases, only a few IVF cycles are paid for, irrespective of the stimulation dose. Because of this, many couples choose high-dose stimulation in the hope of a higher cumulative success rate. However, a rethink is also taking place here. In Germany, for example, some health insurers already pay for unstimulated IVF cycles, and in Switzerland there are signs that NC-IVF therapies will become an elementary part of IVF reimbursement by health insurers.

However, NC-IVF and minimal stimulation IVF treatments will never be able to replace high-dose gonadotropin-stimulated IVF treatments, as these are still more beneficial in several cases. All these IVF therapies are therefore to be understood as complementary techniques with different indications, which together enable an individualised and thus optimal IVF therapy with low risks and high success rates [2].

The International Society for Mild Approaches in Assisted Reproduction, ISMAAR, has been advocating a lower stimulation dose since 2007. ISMAAR has published several position papers summarising and evaluating the above-mentioned positive effects of lower stimulation doses [3].

Every reproductive physician and embryologist should be aware that these therapies are independent forms of therapy. Transferring the logistics of conventional IVF therapy without reflection to NC-IVF or minimal stimulation IVF therapy leads to frustration for all involved and makes it impossible to realise the full potential of these therapies.

Because of this, the idea was born to provide reproductive health professionals and embryologists with practical guidance from centres specialising in NC-IVF and/or minimal stimulation IVF therapies.

Since a basic understanding of reproductive endocrinology is essential for NC-IVF or minimal stimulation IVF, this book first teaches the endocrinological and technical principles relevant to IVF, and only then, based on this knowledge, explains the practically relevant therapeutic procedures. The topic is rounded off by chapters such as costs, risks, history of NC-IVF and minimal stimulation IVF and their future prospects.

The aim of the book is to provide the widest possible expertise. As a result, specialists from different centres, from different continents such as Europe, Asia and North America and thus from regions with different cultural, financial and health

policies have agreed to present their clinical-practical strategies in order to adapt NC-IVF and minimal stimulation IVF therapy to local conditions and so that it can be performed worldwide.

The representatives of these centres are sure that every reproductive specialist who gets involved with these techniques and offers them to many couples, instead of only using them as a stopgap in desperate cases, will be amazed and enthusiastic about the potential these techniques have.

I hope you enjoy reading the book and implementing the contents in your fertility centre.

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# Contents

## Part I Basics

<b>1</b>	<b>How to Use This Book</b> . . . . .	<b>3</b>
	Michael von Wolff	
<b>2</b>	<b>Definitions for Natural Cycle and Minimal Stimulation IVF</b> . . . . .	<b>7</b>
	Michael von Wolff	
<b>3</b>	<b>Indications for Natural Cycle and Minimal Stimulation IVF</b> . . . . .	<b>11</b>
	Michael von Wolff	
<b>4</b>	<b>History of Natural Cycle and Minimal Stimulation IVF</b> . . . . .	<b>15</b>
	Michael von Wolff	

## Part II Physiology

<b>5</b>	<b>Folliculogenesis</b> . . . . .	<b>31</b>
	Michael von Wolff	
<b>6</b>	<b>Ovulation</b> . . . . .	<b>45</b>
	Michael von Wolff	
<b>7</b>	<b>Oocytes</b> . . . . .	<b>59</b>
	Michael von Wolff	
<b>8</b>	<b>Luteal Phase</b> . . . . .	<b>67</b>
	Michael von Wolff	
<b>9</b>	<b>Endometrium</b> . . . . .	<b>75</b>
	Michael von Wolff	

## Part III Clinical Practice

<b>10</b>	<b>Timing of Aspiration in Natural Cycle and Minimal Stimulation IVF</b> . . . . .	<b>93</b>
	Michael von Wolff	

**11 Inhibition of Premature Ovulation in Natural Cycle and Minimal Stimulation IVF** ..... 105  
Michael von Wolff

**12 Ovulation Triggering in Natural Cycle and Minimal Stimulation IVF** ..... 115  
Michael von Wolff

**13 Follicle Aspiration in Natural Cycle and Minimal Stimulation IVF** ..... 125  
Michael von Wolff

**14 Luteal Phase Support in Natural Cycle and Minimal Stimulation IVF** ..... 135  
Michael von Wolff

**15 Treatment Protocols for Natural Cycle and Minimal Stimulation IVF** ..... 147  
Michael von Wolff, Keiichi Kato, and John Zhang

**16 Laboratory Aspects of Natural Cycle and Minimal Stimulation IVF** ..... 165  
Markus Montag

**Part IV Costs, Risks and Success Rates**

**17 Risks of Natural Cycle and Minimal Stimulation IVF** ..... 173  
Michael von Wolff

**18 Costs for Natural Cycle and Minimal Stimulation IVF** ..... 179  
Michael von Wolff

**19 Success Rates of Natural Cycle and Minimal Stimulation IVF** ..... 185  
Michael von Wolff and Isotta Magaton

**Part V Children’s Health**

**20 IVF-Related Children’s Health Risks** ..... 199  
Michael von Wolff

**21 Natural Cycle and Minimal Stimulation IVF-Related Children’s Health Risks** ..... 211  
Michael von Wolff

**22 Asthma and Breastfeeding After IVF** ..... 219  
Michael von Wolff

**Part VI Miscellaneous**

**23 Biopsychosocial Aspects of Natural Cycle IVF/Minimal Stimulation IVF** . . . . . 227  
 Annemarie Schweizer-Arau

**24 Future Aspects of Natural Cycle and Minimal Stimulation IVF** . . . . . 239  
 Michael von Wolff

**Part VII Worldwide Programs**

**25 Natural Cycle IVF and Minimal Stimulation IVF Worldwide** . . . . . 245  
 Michael von Wolff

**26 Germany, Switzerland, Austria—IVF-Naturelle® Network** . . . . . 249  
 Michael von Wolff

**27 United States—Mini IVF®** . . . . . 259  
 John Zhang

**28 Japan—Kato Ladies Clinic** . . . . . 261  
 Keiichi Kato and Satoshi Ueno

**Part VIII Case Discussions**

**29 Andrological Infertility—Case Discussion and IVF Treatments Suggested by Different Centres** . . . . . 273  
 Michael von Wolff and Keiichi Kato

**30 Idiopathic Infertility—Case Discussion and IVF Treatments Suggested by Different Centres** . . . . . 277  
 Michael von Wolff and Keiichi Kato

**31 Increased Age—Case Discussion and IVF Treatments Suggested by Different Centres** . . . . . 281  
 Michael von Wolff and Keiichi Kato

**32 Low Ovarian Reserve—Case Discussion and IVF Treatments Suggested by Different Centres** . . . . . 285  
 Michael von Wolff and Keiichi Kato

**33 Endometriosis—Case Discussion and IVF Treatments Suggested by Different Centres** . . . . . 289  
 Michael von Wolff and Keiichi Kato

**34 Luteal Phase Minimal Stimulation IVF** . . . . . 293  
 John Zhang

# Editor and Contributors

## About the Editor

**Michael von Wolff** is a reproductive physician and the head of the university-based IVF centre in Berne, Switzerland. He has set up a large programme of natural cycle IVF and minimal stimulation IVF in Germany, Switzerland and Austria. His main goal was to optimize and introduce these techniques in many centres due to their manifold advantages. To achieve this goal, he published this practical guide, based on around 30 studies from his centre and based on the expertise of other specialists from Japan and the United States, such as K. Kato and J. Zhang. This guide allows any reproductive physician and embryologist to better understand, introduce and optimize these techniques.

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# Abbreviations

AFC	Antral follicle count
AMH	Anti-mullerian hormone
ART	Assisted reproductive technologies
BMI	Body mass index
CI	Confidence interval
cIVF	conventional IVF (IVF with high-dose gonadotropin stimulation)
COC	Cumulus oophorus complex
d	day
D	Day
E2	Oestradiol
ESHRE	European Society of Human Reproduction and Embryology
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GnRHa	Gonadotropin-releasing hormone agonist
GnRHant	Gonadotropin-releasing hormone antagonist
h	hour
HCG	Human chorionic gonadotropin
HMG	Human menopausal gonadotropin
ISMAAR	International Society for Mild Approaches in Assisted Reproduction
ICSI	Intracytoplasmic sperm injection
IL	Interleukin
IU	International unit
IUI	Intrauterine insemination
IVF	In vitro fertilisation (includes fertilisation by insemination and by intracytoplasmic sperm injection)
LGA	Large-for-gestational-age
LH	Luteinising hormone
NC-IVF	Natural cycle IVF
NSAID	Non-steroidal anti-inflammatory drug
OHSS	Ovarian hyperstimulation syndrome
OR	Odds ratio

P4	Progesterone
PCOS	Polycystic ovary syndrome
PG	Prostaglandin
PGT	Preimplantation genetic testing
PGT-A	Preimplantation genetic testing for aneuploidy
POI	Premature ovarian insufficiency
RNA	Ribonucleic acid
RR	Relative risk
SD	Standard deviation
SGA	Small-for-gestational-age



# **Part I**

## **Basics**

# Chapter 1

## How to Use This Book



Michael von Wolff

### 1.1 Background

The book “Natural Cycle IVF and Minimal Stimulation IVF—from physiology to clinical practice” was written to enable other reproductive health professionals to perform natural Cycle IVF and minimal stimulation IVF treatments effectively. For conventional, i.e. gonadotropin-stimulated IVF, there are fixed stimulation protocols that are easy to apply. However, natural cycle IVF and minimal stimulation IVF require individualisation of the treatment protocols, therefore the use of fixed treatment protocols is only of limited use. Good knowledge of physiology and reproductive endocrinology, as well as a different set of aspiration needles, medications and logistics are also required.

Because of this, it makes sense that you approach the subject matter systematically to have the best sense of achievement and chances of success. In the following we will show you how the book can support this process.

### 1.2 The Thorough Systematic Approach

The thorough systematic approach follows the principle of “to put the cart behind the horse”. This means that you first familiarise yourself with the basics and background and then plan the first therapy. The book has been structured accordingly. It would therefore be best if you first read the book in chronological order from beginning to end, which might take a weekend, and only then start.

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Of course, you have just looked up how many pages the book has and asked yourself how and when you are supposed to finish it. We understand this perfectly, as it is not different for us. Nevertheless, we maintain that a thorough systematic approach would be the best way.

However, if you are too busy to read the whole book, we have put together a fast-track programme below that will get you started in 10 steps, which might just take a few hours.

### 1.3 The (Supposedly) Quick Approach in 10 Steps

The quick approach follows the principle: “to put the cart before the horse”. This means that you follow the ten steps below and as the 8th step you read the chapter “Treatment protocols”. You will select a protocol and start the treatment. The treatment protocols are then adjusted during the course of the treatment. However, it remains to be seen whether this is really the faster way. Natural cycle IVF and minimal stimulation IVF therapy that satisfies the patient and the doctor, and is even enjoyable, always requires an understanding of the basics.

#### The 10 Most Important Chapters for a Quick Approach

1. Chapter “How to use this book?”

Well done. You have already completed this most important step by opening this central chapter. Stay tuned and follow the further chapter suggestions.

2. Chapter “Definitions”

This chapter gives you an overview of how natural cycle IVF and minimal stimulation IVF are defined in the book. You should know what we are actually talking about in the chapters.

3. Chapter “Indications”

This chapter gives you an orientation for whom natural cycle IVF and/or minimal stimulation IVF is indicated and for whom it is not. The viewpoint of the editor is presented. This is relevant because frustration is inevitable if natural cycle IVF is only offered to women with a very poor prognosis and therefore as a last straw. Natural cycle IVF is also unlikely to help a 42-year-old woman with a high ovarian reserve who wants to undergo natural cycle IVF after several frustrating conventional IVF treatment cycles.

4. Chapter “Laboratory aspects”

Monofollicular (natural cycle IVF) or oligofollicular (minimal stimulation IVF) requires laboratory processes that are adapted to the low oocyte count. For example, in monofollicular IVF, no oocyte may be retrieved, which negates all the preparations made by the laboratory. Follicular flushing is also useful in many cases, which must be prepared by the laboratory. You should therefore involve your embryologist and the laboratory in your considerations and planning. A disgruntled and therefore rebellious laboratory is no fun.

### 5. Chapter “Costs”

Natural cycle IVF and minimal stimulation IVF are cheaper per treatment cycle. However, you should calculate the costs over approx. 3 treatment cycles to enable a comparison with conventional IVF. IVF therapies also have special billing requirements. If only one oocyte is retrieved and it is successfully fertilised, but degenerates shortly before transfer, then you need to decide whether the entire laboratory process should be charged to the couple. From a laboratory point of view it is correct, but from a patient motivation point of view it is very awkward. A mixed calculation is conceivable, for example, in which the laboratory costs are only incurred if a transfer is also achieved. These things have to be clarified in advance, especially if you have an economist or a CEO breathing down your neck.

### 6. Chapter “Success rates”

A central point in counselling the couple is the success rate. This must be calculated individually based on the medical history. However, it makes sense not to calculate it per cycle, but per three-month therapy interval. This is because in three months you carry out three natural cycle IVF or minimal stimulation IVF treatments, whereas you would only manage around one conventional IVF treatment in this period. This procedure also allows a cross-comparison with conventional IVF therapy.

### 7. Part VIII “Case discussions”

The procedure for natural cycle IVF or minimal stimulation IVF therapy is not standardised, but depends on the medical history and the cause of infertility. It is therefore useful to look at the procedures suggested by other centres/networks and then decide how to proceed with your couple. We have chosen leading centres/networks to give room not only for different treatment philosophies, but also for different cultures.

### 8. Chapter “Treatment protocols”

If you have decided to perform natural cycle IVF or minimal stimulation IVF, turn to this chapter and choose one of the treatment protocols. The descriptions are detailed and geared towards clinical practice, so the protocols should be a good guide.

### 9. Chapter “Follicular aspiration”

The chapters on “Physiology” (Part II) and on “Technical aspects” (Part III) can be put on hold if necessary. You must, however, read the chapter on “Follicular aspiration”. Follicular aspiration in mono- or oligofollicular IVF is quite different from that in conventional IVF. Or rather, it should be different. To perform analgesia or anaesthesia for 1–2 follicles is as nonsensical as a follicle aspiration for 1–2 follicles with a thick puncture needle commonly used in conventional IVF.

#### 10. The other chapters

With this minimal programme, you can certainly carry out a first natural cycle IVF or minimal stimulation IVF treatment cycle. However, after this first treatment cycles at the latest, you should also turn to the other chapters.

The biggest mistake is to assume that natural cycle IVF or minimal stimulation is “small IVF” in the sense of “simple IVF”. For the woman it is certainly simple, but for the reproductive physician it can be intellectually and logistically challenging.

# Chapter 2

## Definitions for Natural Cycle and Minimal Stimulation IVF



Michael von Wolff

### 2.1 Background

The first IVF treatment in the world was natural cycle IVF. Shortly after, different stimulation treatments were introduced, and new names were coined for the various IVF therapies. Most physicians understand IVF therapies as treatments with gonadotropin stimulation at a dosage of usually 150–300 IU per day. Such stimulation generates a sufficient number of oocytes to allow a high chance of success with low risks. The stimulation protocols have been widely evaluated and standardised. Since these IVF stimulations have been used for years, they can be referred to conventional IVF treatments.

However, no uniform definitions are used for IVF treatments without or with a lower level of stimulation. This makes these IVF treatments confusing and difficult to compare. Because of this, various definitions of IVF treatments without or with a low level of stimulation are presented in this chapter and the definitions used specifically in this book are described.

### 2.2 Definitions According to ISMAAR, 2007

The International Society for Mild Approaches in Assisted Reproduction (ISMAAR) (<http://www.ismaar.org/>) was founded in 2007. It promotes a more physiological, less drug-oriented, lower risk, less expensive and more patient friendly approach to

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**Table 2.1** Definitions, aims and methodology of IVF treatments according to the International Society for Mild Approaches in Assisted Reproduction, ISMAAR [1]

Treatment	Aim	Methodology
<b>Natural cycle IVF</b>	1 oocyte	No medication.
<b>Modified natural cycle IVF</b>	1 oocyte	HCG, FSH/HMG only as add back if GnRH antagonists are used.
<b>Mild IVF</b>	2–7 oocytes	GnRH antagonists, low dose FSH/HMG, oral compounds.
<b>Conventional IVF</b>	≥8 oocytes	GnRH agonist or antagonists, conventional FSH/HMG dose.

assisted reproduction embracing not only natural cycle treatment, but also mild stimulation protocols and in vitro maturation of oocytes [1].

ISMAAR had proposed a terminology for ovarian stimulation for IVF in 2007. The terminology, aim and methodology are shown in Table 2.1. The terminology of ISMAAR is basically very good, but shows some weaknesses in clinical practice.

According to ISMAAR, natural cycle IVF is defined as treatment without any medication, i.e. without an ovulation trigger and without individual doses of GnRH antagonists or non-steroidal anti-inflammatory drugs (NSAID). In practice, however, this makes little sense, as natural cycle IVF therapy cannot be carried out effectively without such medication.

According to ISMAAR, modified natural cycle IVF includes gonadotropin stimulation if GnRH antagonists are also given. This raises the question of whether the term “natural cycle” is still justified with the administration of gonadotropins.

Mild IVF is defined by ISMAAR as IVF therapy with gonadotropin stimulation of up to 150 IU per day administered as part of an antagonist cycle. According to the publications from the last few years, an IVF with approx. 150 IU gonadotropin is referred to as mild IVF in almost all studies. The studies compared a mild IVF with mostly 150 IU gonadotropin with a conventional IVF with >150 IU [2].

What is missing from the terminology is a term for very mild stimulations that do not require a fixed antagonist protocol and that can be performed logistically like natural cycle IVF, i.e. without analgesia or anaesthesia during the follicle aspiration.

### 2.3 Definitions According to the International Glossary on Infertility and Fertility Care, 2017

A group of 25 professionals from all parts of the world set up a consensus-based and evidence-driven set of 283 terminologies used in infertility and fertility in 2017 [3]. The terminology developed by the expert group is presented in Table 2.2.

The definitions in the International Glossary on Infertility and Fertility Care are relatively well suited for clinical practice, but also have a few weaknesses.

**Table 2.2** Definitions according to the International Glossary on Infertility and Fertility Care, 2017 [3]

Treatment	Definition
<b>Natural cycle IVF</b>	An ART procedure in which one or more oocytes are collected from the ovaries during a menstrual cycle without the use of any pharmacological compounds.
<b>Modified natural cycle IVF</b>	An ART procedure in which one or more oocytes are collected from the ovaries during a spontaneous menstrual cycle. Pharmacological compounds are administered with the sole purpose of blocking the spontaneous LH surge and/or inducing final oocyte maturation.
<b>Mild ovarian stimulation IVF</b>	A protocol in which the ovaries are stimulated with gonadotropins, and/or other pharmacological compounds, with the intention of limiting the number of oocytes following stimulation for IVF.

Even with this terminology, a natural cycle IVF (ART) therapy is understood as a treatment without any medication. However, such an IVF, i.e. an IVF without an ovulation trigger, cannot be effectively implemented.

This terminology also lacks a term for very light stimulations that do not require a fixed antagonist protocol and that can be performed logistically like a natural cycle IVF, i.e. without analgesia or anaesthesia during the follicle aspiration.

## 2.4 Terminology Used in This Book

In this book, an attempt is made to use basically modified definitions of the already established terminology from ISMAAR and the International Glossary on Infertility and Fertility Care. The definitions used here are derived from the developments in the field of these IVF techniques (see Chap. 4, Fig. 4.2). However, they had to be adapted to the requirements of everyday clinical practice (Table 2.3).

The main difference is that “Natural cycle IVF” is defined as any IVF with natural folliculogenesis and a mostly natural luteal phase, but with the inclusion of medication to prevent premature ovulation. Since folliculogenesis is not relevantly influenced by medication to prevent premature ovulation, no luteal phase support is required (see Chap. 8). The definition of “Natural cycle IVF” thus corresponds to the “Modified Natural cycle IVF” of the “International Glossary on Fertility and Fertility Care” presented in Table 2.2.

The term “Minimal stimulation IVF” was also introduced. This term refers to treatments with light stimulation, be it with clomiphene citrate, aromatase inhibitors or gonadotropins with a dose of  $\leq 100$  IU per day. The aim of this light stimulation is to grow fewer oocytes without analgesia/anaesthesia and to perform monthly cycles. Cryopreservation is usually not necessary.

Conventional IVF is defined as all gonadotropin stimulations with a stimulation dose of  $\geq 150$  IE per day. Conventional IVF treatments usually require anaesthesia during aspiration and all aim to retrieve a relatively large number of oocytes, carry



**Table 2.3** Principles, aims and methodology of IVF treatments used in this book

Treatment	Principle	Aim	Methodology
<b>Natural cycle IVF</b> (Modified natural cycle IVF according to the International Glossary terminology, Table 2.2).	Monofollicular IVF	1 oocyte; aspiration without analgesia/ anaesthesia	Medication to trigger ovulation or to avoid premature ovulation (low dose clomiphene citrate, NSAIDs, single injections of GnRH antagonists); usually no luteal phase support.
<b>Minimal stimulation IVF</b>	Oligofollicular IVF	1–3 oocytes; aspiration usually without analgesia/ anaesthesia.	Stimulation with clomiphene citrate, aromatase inhibitors, gonadotropins $\leq 100$ IU per day; GnRH antagonists only if required; luteal phase support.
<b>Conventional IVF</b> (Includes mild IVF according to ISMAAR, Table 2.1, and the International Glossary terminologies, Table 2.2).	Polyfollicular IVF	$>3$ oocytes; aspiration mostly with analgesia/ anaesthesia.	Gonadotropin stimulation $\geq 150$ IE gonadotropin per day; GnRH agonists or GnRH antagonist protocols or progestin-primed ovarian stimulation (PPOS); luteal phase support.

out embryo selection, preserve surplus embryos and allow preimplantation genetic testing for aneuploidy (PGT-A) if necessary.

In summary,

The definitions proposed worldwide are basically good, but they are of limited applicability for clinical practice when performing natural cycle IVF treatments and IVF treatments with minimal stimulation. Therefore, slightly adapted definitions are used in this book. It should be noted that the definitions from the centres “Kato Ladies Clinic, Tokyo, Japan” and “New Hope Fertility Center, New York, United States” may differ somewhat (for centre-specific definitions see chapters in “Part VII, Worldwide programs”).

## References

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# Chapter 3

## Indications for Natural Cycle and Minimal Stimulation IVF



Michael von Wolff

### 3.1 Background

In a review article about natural cycle IVF published in 2019 [1], von Wolff concluded that “Natural Cycle-IVF and conventional gonadotropin stimulated IVF are basically different forms of treatment .... The treatments should not compete with each other but should be seen as complementary”.

This statement applies not only to natural cycle IVF, but also to minimal stimulation IVF treatments and, of course, conventional IVF treatments. In practical terms, this means that the indications for the treatments are partly the same, some of indications overlap and some indications apply exclusively to only one of the therapies.

This becomes particularly clear with the following two examples:

In a woman with an incipient premature ovarian insufficiency with increased FSH concentrations but still regular cycles, conventional IVF does not make sense. On the other hand, in a 42-year-old woman with a still high ovarian reserve, NC-IVF does not make sense.

An indication for IVF therapy is made based on the individual medical requirements. However, the indication is also influenced by the couple's wishes, the logistical possibilities of the centre and the regional or personal cultural circumstances. Thus, the indication for or against a specific IVF therapy is made up of several factors. In this chapter, the factors that speak for, but also against one of the therapies are presented.

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**Natural Cycle IVF is Especially Suitable If:**

- Good prognostic factors (female age ca. <38 years, short duration of infertility, andrological infertility)
- Regular cycles
- Follicle aspiration without analgesia/anaesthesia possible
- Ovaries for aspiration easily accessible
- Longer time to pregnancy acceptable
- High risk with gonadotropin stimulation (thrombosis, lupus erythematosus, etc.)
- Poor responder with very low ovarian reserve

**Natural Cycle IVF is Rather Not Suitable If:**

- Bad prognostic factors (female age ca.  $\geq 40$  years, idiopathic infertility, several previous IVF treatments and embryo transfers without pregnancies) in combination with still high ovarian reserve
- Irregular cycles
- Follicular aspiration very painful, requiring analgesia/anaesthesia
- Ovaries for aspiration hardly accessible

**Minimal Stimulation IVF is Especially Suitable If:**

- Good prognostic factors (female age ca. <38 years, short duration of infertility, andrological infertility)
- Follicle aspiration without analgesia/anaesthesia possible
- Ovaries for aspiration easily accessible
- High risk with gonadotropin stimulation (thrombosis, lupus erythematosus, etc.)
- Poor responder with very low ovarian reserve

**Minimal Stimulation IVF is Rather Not Suitable If:**

- Bad prognostic factors (female age ca.  $\geq 40$  years, idiopathic infertility, several previous IVF treatments and embryo transfers without pregnancies) in combination with still high ovarian reserve
- Follicular aspiration very painful, requiring analgesia/anaesthesia
- Ovaries for aspiration hardly accessible
- Wish not to use hormone injections

**Conventional IVF is Especially Suitable If:**

- Bad prognostic factors (female age ca.  $\geq 40$  years, idiopathic infertility, several previous IVF treatments and embryo transfers without pregnancies) in combination with still high ovarian reserve
- Preimplantation genetic testing (PGT) required

**Conventional IVF is Rather Not Suitable If:**

- Low ovarian reserve
- Poor responder
- High risk with gonadotropin stimulation (thrombosis, lupus erythematosus etc.)
- Wish not to use hormone injections

**Practical Conclusions**

- The indication for IVF therapy is influenced by the individual medical conditions, the wishes of the couple, the logistical possibilities of the centre and the regional or personal cultural circumstances.
- The indications for the different treatments are partly the same but can also overlap. There are also indications that apply exclusively to one of the therapies.
- The indication for one of the IVF therapies must be made individually and may change during the course of the IVF therapy.

**Reference**

1. von Wolff M. The role of natural cycle IVF in assisted reproduction. *Best Pract Res Clin Endocrinol Metab.* 2019;33:35–45.