HUMAN FERTILITY and INFERTILITY
From PREHISTORY to the PRESENT

This book is dedicated to
Josée Bergans en Kristin Wouters:
women, mothers and grandmothers.

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Sterck & De Vreese

TABLE of CONTENTS

Habsburg family portrait with emperor Maximilian I, his wife, his son, two grandsons and a granddaughter (ca. 1515) by Bernard Strigel (1460-1528), Kunsthistorisches Museum, Vienna (Austria).

PREFACE

Dear reader,
The European Association of Urology is pleased to present you this book as a sign of gratitude for attending our 40th Annual Congress in Madrid. The chairman of the EAU History Office, together with his eldest daughter, has put together an attractive volume on topics with which urologists obviously have an affinity, but in which we are often underrepresented.

The perspectives on human fertility and infertility have differed greatly based on cultural norms and sensitivities across time, but also geographically. This book reminds us of how these aspects of human life have been experienced over time and how new discoveries have increased our knowledge, sometimes based on incidental findings, but more often as a result of basic and clinical research. These developments have significant consequences for the diagnosis and therapy of female and male patients with fertility problems.

The book focuses not only on medical aspects of human reproduction but also deals with the psychological and social aspects of pregnancy, birth and parenthood. The different chapters have something to offer for every reader, as a urologist but also as a human being, and make this a publication of general interest, and at times also quite surprising and even intriguing.

Philip Van Kerrebroeck is widely recognized as a leader in the field of functional urology and has published extensively in the scientific medical literature. In recent years his interests extended towards the history of urology, and he has written previously on topics where culture, history and urology overlap. The special combination of developing and writing this book together with his daughter, a reproductive gynaecologist, allows for a multidisciplinary and up-to-date view on human fertility and infertility. This book is a culmination of knowledge on the medical aspects but also offers us a unique historic perspective on human fertility and infertility.

Congratulations on behalf of our Association to Philip and Helena for putting together: *Human FERTILITY and INFERTILITY. From prehistory to the present.*

We hope that you, members of the EAU, will enjoy reading this book.

Arnulf Stenzl
EAU Secretary General
Professor of Urology, University of Tűbingen, Germany

Family portrait, painting (1621) by Anthony Van Dyck (1599-1641), Hermitage Museum, Saint Petersburg (Russia).

FOREWORD

Dear reader,
It is with great pleasure that we introduce this special publication on human fertility and infertility. This book is offered as a valuable resource and reflects our commitment to advance understanding in a field that has historically been underexplored, but holds critical importance for millions of men, women, and families worldwide.

Human infertility, once a topic whispered about behind closed doors, has gradually emerged from the shadows of stigma and misinformation. This book takes us on a comprehensive journey through the complex causes, diagnostic advances, and treatment options that are reshaping the landscape of both male and female reproductive health.

The chapters approach a wide range of issues, from the latest scientific discoveries to the social and psychological impact of infertility. Readers will find expert perspectives that highlight the challenges men and women face, along with the innovative solutions that are now within reach.

Professor Philip Van Kerrebroeck and Dr Helena Van Kerrebroeck-Gijbels have skilfully created a resource that is both informative and empathetic. Their dedication to increase both understanding and compassion in this field is evident on every page.

This publication is not only interesting for urologists and fertility specialists, but also for anyone involved in the broader discussions on reproductive health, societal expectations in the field of human reproduction, and the evolving definitions of family and parenthood.

We are confident that this book will be a valuable addition to your library, sparking meaningful conversations and inspiring a deeper understanding of male and female fertility and infertility. We hope you enjoy the information offered and will find ways to share this knowledge with your colleagues, patients, family, friends and the wider community.

With warm regards,

Carlo Bettocchi
Chairman EAU Section of Andrological Urology
Professor of Urology, University of Foggia, Italy

The Arnolfini portrait (1434) by Jan Van Eyck (ca. 1390-1441), National Gallery, London (UK).

1 INTRODUCTION

Happiness is the ultimate end and purpose of human existence.

Aristotle (384–322 BCE), ancient Greek philosopher and polymath.

Human FERTILITY and INFERTILITY

Fertility is one of the most important drivers of human life and the result, procreation, can even be considered as *the* purpose of life and a major source of happiness. Hence, the history of fertility is the history of mankind. Indeed, since the dawn of humanity, fertility has played a major role in human thought, culture, and activities. The mystery of reproduction was one of the earliest dilemmas facing the human race, as for a good part of our early history, humans did not understand how a woman became pregnant. Therefore, the discovery of the relation between sexual intercourse and pregnancy must have been one of the most surprising early concepts acquired by the human brain.

Fertility in demographic context refers to the ability to have offspring rather than the physical capability to reproduce, which is termed fecundity. The antithesis of fertility is infertility, while the antithesis of fecundity is sterility. In medicine, fertility refers to the ability to have children and infertility or subfertility is defined by the World Health Organization (WHO) as the failure to achieve clinical pregnancy after twelve months of regular, unprotected sexual intercourse. Fertility rate is the average number of children born during an individual's lifetime.

Since the beginning of the 20th century, and in a remarkably short time, major additional discoveries related to human reproduction were made. These allowed to uncover the basic principles of human fertility and included the understanding of the hypothalamic-pituitary-ovarian axis, the discovery of gonadotrophins, the isolation of gonadal steroids, the detection of the hormonal changes involved in the control of the menstrual cycle, culminating in the success of in vitro fertilization and its allied techniques. These new physiological and pathophysiologic insights also allowed for understanding

the causes of human infertility and were the basis for modern and specific therapies in case of infertility.

Human infertility is an important physical and mental health problem and has a major negative impact on the quality of life of both the female and the male partner. This negative impact can even be lifelong if the fertility problem cannot be solved.

Parenthood is an instinct-driven physiological experience, as there is an inherent and deep-seated desire in most adult females, but also in most men, to have a child. Instinct of parenthood is a powerful desire present in all living creatures, including humans. New social models opened the way for alternative forms of maternity and paternity, independent of the relational status of the mother and the father. New fertilization techniques even disconnected procreation from sexual intercourse between a biological female and male.

Reproduction is unique in many ways, and it performs a very important role in the process of immortality. Inability to have children is considered universally as a personal failure and tragedy. Infertility does not end a person's life, but it can have a devastating impact on the individual's life for not fulfilling their biological role of maternity and paternity.

Obviously, human fertility and infertility, as important human phenomena, may give rise to several questions. How was and is human fertility and infertility perceived in different geographical areas and cultures? How have people dealt with fertility problems in the past and how do they nowadays? What led to the discovery of the mechanisms of fertility and what made infertility treatable? Which discoveries allowed to explain the mechanisms of pregnancy and how did birthing evolve based on fundamental and clinical research? What is the historic perspective of infertile couples and what were the therapeutic modalities in the past? Which new therapeutic modalities are available in case of subfertility or infertility? How did parenthood develop from prehistory to the present time?

Infertility in humans is a global and prevalent health concern, impacting an estimated 10–15% of couples worldwide. Male factors contribute to approximately 20% in infertile couples and coexist with female factors in an additional 40%. Nevertheless, despite the worldwide medical attention to female factors, fewer men seek fertility solutions as compared to women.

Human INFERTILITY and the UROLOGIST

Although infertility can result from both male and female factors, there is still a widespread misconception that infertility is predominantly a female issue, overshadowing the importance of male factors. Obviously, the male factor is important in human infertility, but the need to refer males for further evaluation is still overlooked in a significant number. This discrepancy highlights the need for increased awareness and a more comprehensive engagement of urologists in the assessment and management of male infertility, even in the current era of assisted reproductive technology (ART). Indeed, ART, including encompassing techniques as in vitro fertilization (IVF), intracystoplasmatic insemination (ICSI) and gamete intrafallopian transfer (GIFT), has revolutionized reproductive medicine by providing a path to parenthood for those struggling with fertility problems, but unfortunately has further decreased the involvement of reproductive urologists, and sometimes provides a short-circuit that neglects specific possibilities in treating male infertility.

Over the past half-century, a steep decline in human fertility rates has been recorded worldwide and in nearly every country. This universally reduced fertility is being driven by increasing prosperity, largely through the mediation of social factors, the most powerful of which are the education of women and an accompanying shift in life's purpose, away from procreation. In addition, it is clear that environmental and lifestyle factors also have a profound impact on human reproductive competence, particularly in the male, where increasing prosperity is associated with a secular decline in semen quality and testosterone levels. Additionally, sedentary behaviour, obesity and substance abuse contribute to the decrease in male fertility. It stresses the significance, in case of fertility problems, to conduct an evaluation process involving both male and female partners, to identify any underlying factors contributing to infertility, but also to identify patients who do not require any interventions beyond ART.

We should recognize that the increased prosperity associated with the demographic transition greatly reduces the selection pressure on high fertility genes by lowering the rates of infant and childhood mortality. The retention of poor fertility genes within the human population is also being exacerbated by the increased uptake of ART. It is arguable that all of these elements are colluding to drive our species into an infertility trap. If we are to avoid this trap, it will be important to recognize the factors contributing to this phenomenon and adopt the social, political, environmental, and lifestyle changes needed to bring this situation under control.

Hence, there remains a pivotal role for urologists in cooperation with gynaecologists, andrologists, endocrinologists and other reproductive specialists in the evaluation and treatment of male infertility. Urologists have the expertise to diagnose reversible causes of male infertility, such as varicoceles, ejaculatory duct obstruction and hormonal imbalances, and can perform surgical techniques such as varicocelectomy and testicular sperm retrieval to enable ART. Additionally, they can provide advice on lifestyle modifications and prescribe appropriate medications to enhance fertility outcomes.

Although the role of urologists in the era of ART is important, several barriers limit their involvement, such as the limited availability and distribution of specialized andrological urologists, definitely in some countries or regions. Additionally, the lack of awareness and education among healthcare professionals and the general population about the role of urologists in male infertility contributes to the underutilization of their services. In some countries financial constraints, including the absence of health insurance coverage for infertility diagnosis and treatment, also pose significant barriers to couples seeking care.

From PREHISTORY to the PRESENT

Human FERTILITY and INFERTILITY From prehistory to the present tries to answer the questions raised, by presenting important discoveries in the field of human fertility and infertility and by discussing the role of andrological urologists and reproductive gynaecologists in diagnosing and treating fertility problems in view of historic achievements. This perspective includes a look at therapies in case of reversible causes, but also in performing surgical interventions for structural or anatomical abnormalities.

However, this book is not a medical textbook. The different chapters present a narrative review of historic aspects of human fertility and infertility and are illustrated with informative and relevant, but sometimes surprising and unique images. There may be some overlap between the different chapters as this allows individual reading of the chapters in whatever order.

With this book we aim at stimulating the interest of urologists in human fertility and optimize their role in the evaluation and treatment of women and men with fertility problems, by presenting facts and figures in a historical perspective, indeed from prehistory to the present.

For our urological colleagues without a specific andrological sub- or superspecialization or interest, we hope that this book is an interesting read and can be an enjoyable way to appreciate the intriguing and sometimes enigmatic aspects of human fertility and infertility.

Royal urological fertility problems?

Throughout history several royal couples suffered from a (temporary) fertility problem due to a male urological abnormality, although initially the inability to conceive was rather attributed to the female partner.

The French King Louis XVI (1754–1793) **[1]** and his wife Marie Antoinette (1755–1793) **[2]** are a famous example of presumed royal infertility due to a penile problem. The later king, born Louis Auguste, was the grandson of King Louis XV of France and became dauphin (successor to the throne) after the death of his father, the former dauphin Louis (1729–1765). He was a shy boy, easily taken by depression, but on May 16, 1770, he was forced to marry Marie Antoinette, born Archduchess Maria Antonia of Austria, the 15th of 16 children to Austrian Empress Maria Theresa (1717–1780) and her husband the Holy Roman Emperor Francis I (1708–1765).The marriage was a union of two adolescents in an effort to forge a political alliance and was arranged by the French and Austrian monarchs.

After the marriage dinner, the couple was led to a special wedding chamber and spent the night together but without further action. Louis made the following entry for his wedding night in his journal:

'**Rien**.' **(Nothing)**

From the next evening onwards, Louis slept in his own apartment. Some evenings he went to Marie Antoinette's bedroom and tried unsuccessfully to have intercourse with her. Marie Antoinette scarcely possessed the feminine charms needed to thaw a frigid husband and therefore her aunts advised her urgently to respond to the gestures of her husband. The Spanish ambassador wrote one and a half month after the marriage:

'**I have been assured that the royal marriage has not been consummated. The non-consummation is not due to some physical obstacle, but to a kind of moral frigidity which the dauphin's private tutor is trying to mitigate**.'

After three years of marriage, no pregnancy followed and both the French and Austrian courts started to worry, as to conceive a successor was an essential part of the royal duties for a dauphin. Rumours circulated about 'sexual dysfunction' of the future king and the couple's fertility problem was used to desacralize the monarchy. Pamphlets that depicted an 'impotent' Louis were part of the effort which led to the French Revolution and, ultimately, to the King's execution.

The marriage of Louis XVI and Marie Antoinette was only consummated 8 years after the wedding ceremony and this delay could have been due to a genital abnormality, a strict religious upbringing, a difficult childhood, the immaturity of the spouses or a combination of factors that may have inhibited their sexuality. Over the years, vivid discussions took place, whether Louis XVI overcame his sexual problems following a urological intervention (frenulotomy or 'partial' circumcision)

1 *Louis XVI*, portrait painting (1778-1779) by Antoine-François Callet (1741-1823), Palace of Versailles (France).

2 *Marie-Antoinette*, portrait painting (1788) by Élisabeth Louise Vigée Le Brun (1755-1842), Palace of Versailles (France).

or rather as a result of a 'spontaneous' cure. It wasn't until the 19th of December 1778, when the queen gave birth to a daughter, that the rumours were put to rest, as the royal couple's fertility was finally confirmed.

Had Louis Auguste indeed a urological abnormality that was cured with an intervention, or is all this hagiography stimulated by revolutionaries that wanted to weaken and overthrow the monarchy? What are the facts? What happened, or rather, what did not happen, during the 8 years of infertile royal marriage?

On the 16th of July 1770, the dauphin fell ill and a bloodletting was performed by the king's chief surgeon, Germain Pichault de La Martinière (1697–1783). At that occasion Louis XV asked this excellent anatomist to check if his grandson had any 'natural defect' that might prevent the consummation of marriage. La Martinière examined the dauphin and reassured the king that there was no 'anatomical problem'.

On the 8th of August 1770, Marie Antoinette urged her husband to confide in her. Louis assured that he knew what was involved in marriage, but that he had imposed upon himself a temporary 'code of conduct', the term of which had expired, and that he would live with her in the 'greatest intimacy'. But nothing changed and the dauphin continued 'pausing for reflection', requesting more time to 'overcome his fear'. Alarmed, Empress Maria Theresa consulted Gerard van Swieten (1700–1772), chief physician to the Viennese court, asking him if some drug might not prove effective, but the latter responded evasively. Therefore, the empress advised her daughter:

'**Caress, cuddle, but too much haste will ruin everything**.'

On January 23, 1771, Louis confessed to his wife that he had intended to consummate their marriage on their wedding night but was held back by fear that had grown inside him ever since. He also indicated to her that friendship and trust were gaining the upper hand and that he had resolved to obtain for himself the joy of being intimate with her.

From March 21st on, Louis returned to sleep in his wife's bed every night, and according to the 'Journal' of the historiographer Jacob Nicolas Moreau (1717–1803), he may have consummated his marriage on the evening of March 26, 1771. In reality, the attempt was only partly successful since the penetration was incomplete and the Austrian diplomat Florimond Claude (1727–1794) described in a report that:

'**A very minor operation deemed necessary to remove the obstacles preventing the prince from consummating his marriage**.'

On October 28, 1772, King Louis XV summoned the two young spouses and demanded a full account of their progress along the path to conjugal intimacy. The prince declared that he had

'**attempted to consummate his marriage but feelings of pain always prevented him from doing so and he was uncertain whether the pain was caused by a physical abnormality or some other factor**.'

Two days later Louis XV decided to examine his grandson himself, and he found that:

'**The very small obstacle which exists is an extremely common condition in adolescents and does not require an operation**.'

Word soon spread that the dauphin had a small anatomical defect, the nature of which was known in surprising detail. It was said he had

'**phimosis which until recently was of no concern, but that at certain moments it caused pain so sharp that he had to curb his impulses**.'

The dauphin refused to consider surgery, and it would take him another three years to come to a decision. With the death of Louis XV in 1774, Louis and Marie Antoinette became king and queen of France. Now progeny became even more imperative. A letter from a royal confidant, dated August 5, 1774, reports:

'**Some say the frenulum is so short that the prepuce does not retract upon entry, causing His Majesty much pain and forcing him to curtail the movements necessary to complete the act. Others think a tight prepuce prevents the head of the penis from being exposed, making it impossible for His Majesty to have full erections. If it is a matter of a short frenulum, this condition is found in many individuals, causing problems when they first become sexually active. Since most people have a stronger sex drive than His Majesty, they manage with practice, a groan of pain and some good will, to tear the frenulum completely, or sufficiently to keep using it, so that gradually intercourse**

3 *Joseph de Lassone*, portrait painting (1772) by Joseph-Siffred Duplessis (1725-1802), Calvet Museum, Avignon (France).

4 *Catherine de' Medici*, portrait painting (1547-1559) by Germain Le Mannier (act. 1537-1560), Galleria Palatina, Florence (Italy).

becomes normal. But when the patient is timid, the surgeon makes a small incision, relieving the obstacle. If the problem is a tight prepuce, one could resort to an operation which at the king's age is more painful and severe, requiring a kind of circumcision, because if the rough edges of the lips of the incision are not made smooth, intercourse could be impossible.'

Towards the end of 1774, Louis XVI realized that something had to happen and an operation was planned on December 17. Yet the year ended without an intervention. The queen did not seem very optimistic, as she wrote to her mother:

'I strongly doubt that the king has decided to have the operation. Unfortunately, the doctors are confusing him. My doctor thinks the operation is not necessary but could be useful. The king's doctor, who is an old fogy, says that there are many drawbacks to an operation and an equal number of drawbacks in not having it.'

Early 1777 the queen's brother, Joseph II (1741–1790), arrived in France to speak with his brother-in-law. Louis XVI didn't seem embarrassed by the inquiry and willingly described his physical condition. Joseph requested urgent advice and pressed the dauphin to consult the royal physician, Joseph-Marie François de Lassone (1717–1788) **[3]**. Lassone embarked on an extensive interrogation, followed by a detailed examination, eventually even a small intervention. His secret report was never published in full, and Joseph II wrote to the Grand Duke of Tuscany:

'In the end, it's not a weakness of the body or spirit; it's simply that he hasn't had his "let

there be light" moment yet. His technique is still in the process of formation. In his marriage bed, he has strong erections, he inserts his member, remains there for perhaps two minutes without moving, withdraws without ejaculating, and while still erect, bids good night. It's incomprehensible. He sometimes has nocturnal emissions, but always while lying motionless. He's satisfied, saying he does it only out of a sense of duty, but has no desire for it. He should be whipped until he discharges in anger like a donkey. My sister does not have the temperament for this and together they make an utterly inept couple.'

Joseph II left Versailles on May 30, 1777, and two and a half months later Louis XVI confessed to his aunts:

'I delight in the pleasure, and I regret that I wasn't aware of it for so long!'

The Austrian ambassador confirmed this 'most interesting event' that took place on August 22, and describes it as follows:

'The king went to see his wife just as she was finishing her bath; the spouses were together for about an hour and one-quarter; the king demanded a commitment from the queen that what had happened between them remain a secret. The only exception was to be the primary physician, Lassone, who, informed by the king of all the circumstances, did not hesitate to affirm that the marriage had been consummated.'

On the 30th of August, Marie Antoinette too confirmed the happy event, writing to her mother:

'I'm experiencing the most fundamental pleasure. It has been eight days since our marriage was consummated. The act was repeated and yesterday it was more complete than the first time. I don't think I'm pregnant yet, but I wouldn't be surprised if it happened at any moment.'

Most historians confirm that the royal marriage was not consummated until 1777, probably after Louis finally agreed to an operation. His childish naivety may explain why he didn't become aware of this hindrance until very late. On November 14, 1772, the Austrian ambassador confirms that Louis was not impotent, but the expert eye of La Martinière described 'a mysterious condition, extremely common in adolescents. The most probable explanation is a short frenulum or a narrow foreskin, which did not allow full exposure of the glans penis, and likely caused pain and prevented a 'comfortable' sexual penetration.

What remains bizarre is the fact that Louis was not motivated to seek the assistance of a surgeon to help him to fulfil his marital obligation, but on the contrary disregarded for years gibes and snide remarks, even laughs, concerning his 'sexual problem'. Louis initially refused to be operated, because of fear of pain, risk of complications even death, or an unsatisfactory outcome. A frenulotomy, or (partial) circumcision, was even at that time a simple, brief operation, but indeed would have been painful, since done without anaesthesia. Furthermore, any intervention at that time without notion about hygiene, was not without risks and could cause serious infection. Of course,

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