
Role of Folliculo-luteal Function in Human Reproduction

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 Springer

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ISBN 978-3-319-39539-5 ISBN 978-3-319-39540-1 (eBook)
DOI 10.1007/978-3-319-39540-1

Library of Congress Control Number: 2016944621

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*This book is dedicated to the memory of
Ignaz Philipp Semmelweis (1818–1865)
“saviour of mothers”,
the eponym of our university,
on the occasion of the 150th anniversary of his death*

Foreword

I accepted with honour and joy when György Siklósi invited me to write the Foreword to his book titled “Role of Folliculo-luteal Function in Human Reproduction”. I did so also because we worked together in the management of the Hungarian Society of Obstetrics and Gynaecology for more than a decade.

“The rays of the sun, when the figure of Semmelweis is uncovered, will be reflected from the white marble primarily onto us, Hungarian doctors and obstetricians. Let these rays light the ways of truth, the ways that Semmelweis walked; but also let them fire us up for such labour as Semmelweis did: labour after which life and happiness can spring forth” (part of the speech given by Dr. Árpád Bókay on 30 September 1906, at the inauguration of the statue of Semmelweis). After reading the book of Professor Siklósi, we feel struck by the realisation that the author’s life work possesses great, epoch-making importance: it gave rise to novel knowledge, and after it “life and happiness can spring forth”. Beyond his energetic and ambitious working style always dwelled the great love he guided with both his young and experienced colleagues on the often bumpy ways of science.

The immense progress of technical science during the last decades established a great advance in medical science as well. Within the medical areas, these changes are probably most evident in the field of obstetrics. The new diagnostic and therapeutic methods developed by Professor Siklósi establish the basis of a qualitatively new practice in possibly the most important obstetric issues (infertility, spontaneous and habitual miscarriage, preterm birth, intrauterine retardation, preeclampsia, etc.); it opens a whole new world before the reader.

Assuring sufficient number of population is of national interest. The procedures developed and described by the professor are of vital importance in this problem as well. They are vitally important as our homeland is in a demographic crisis. The number of births has been decreasing for years. Since 2000, the number of births fails to reach 100 thousand per year, whereas 120 thousand newborns should be born to maintain the national population. The situation is worsened by the high prevalence of infertility, the high preterm birth rates and the large number of miscarriages and intrauterine growth abnormalities. The work of Professor Siklósi has an incredible significance for this reason: it gives profoundly grounded, effective and successful ways to solve these problems in the clinical practice.

I am convinced that extensive implementation of the methods presented in the book would decisively improve the results, and this would help to stop the

population decline and contribute to the sustenance of the nation and last, but not least, to the joy of families. The question arises: what was the motivational force of this enormous, epoch-making research work that is also of considerable use in the clinical practice? Knowing the results, only one answer is possible. Professor Siklósi has taken on board the unquenchable love for the medical profession and every mother, the strive for true service of the nation and, finally, the thoroughness of the marvellously fruitful scientific area that he created and developed and which helped him to steadily achieve these goals.

I am recommending an excellent book. I definitely recommend reading this book. It contains new, gap-filling information that means very much to the clinical practice, and the adaptation of this knowledge would help us to promote the growth of the nation and the happiness of families. I think that the life course of Professor Siklósi is a fine example of the unselfish servitude of science and healing, as this book justifies as well.

Pécs, Hungary

István Szabó

Preface

Preterm birth, intrauterine growth retardation (IUGR) and preeclampsia (PE) are perhaps the greatest challenges in obstetrics today. Their underlying cause is virtually unknown and thus, treatment and prevention is unresolved. These three complications are responsible for three-quarters of foetal perinatal mortality, they are the leading cause of death, morbidity and disability among newborns and children, and their adverse health consequences affect the entire life. Their significance is further emphasised by the fact that their incidence shows a rising tendency even in developed countries such as the USA: the incidence of preterm births increased from 9.4 to 12.5% between 1981 and 2004. From approximately 140 million births in the world, 15 million end with preterm birth; birth of a retarded newborn occurs in 15 million cases and birth complicated with preeclampsia in 7 million cases per year, and more than 20 million planned clinical pregnancies end up with abortion. About eight million newborns die before the age of one each year, 3.1 million out of which is attributable solely to preterm birth. Mortality in retarded babies is four to eightfold higher compared to eutrophic newborns. Preeclampsia still causes 50,000 deaths among mothers worldwide. With the rapid development of neonatology, survival rate of preterm infants swiftly increased; however, this could not result in the reduction of lifelong adverse health effects of preterm birth and IUGR, and the number of disabled people also increased significantly. Preterm birth and retardation increases the incidence of insulin resistance, glucose tolerance and hypertension as early as prepubertal age or young adulthood. Preterm birth and retardation significantly increase the incidence of coronary diseases, stroke, type 2 diabetes mellitus, obesity, metabolic syndrome and osteoporosis later in life. Recurrent miscarriage or habitual abortion (5% of couples), unexplained infertility (5–6% of couples) and polycystic ovary syndrome (approximately 10% of women) are also unresolved problems. Infertility affects about 72 million couples in the world at any given time. Obviously, we can provide a substantial solution for the problems described above only by appropriate treatment and prevention methods based on the understanding of their underlying causes. The purpose of our work is to give an overview of the causes of these problems as well as the effective methods for their prevention and treatment.

According to international scientific societies on human reproduction and the general view of experts, the confirmed presence of ovulation is sufficient for diagnosing physiological menstrual cycle. The presence and role of luteal insufficiency in human reproduction cannot be demonstrated. Our methods for the prevention and

treatment of the human reproductive disorders described above were based on the recognition of the fact that – contrary to the general concept – a significant proportion of ovulatory cycles are not sufficient for conception and physiological reproduction. This opened the door for a new, unknown field – the very important field of hormonal insufficiency of ovulatory cycles (folliculo-luteal insufficiency) – where new relationships could be found that are very important to study, treat and prevent human reproductive disorders.

The application of our method for the quantitative diagnosis of ovulatory menstrual cycles clearly showed that the most common disorders of human reproduction can be attributed to varying degrees of hormonal insufficiency (FLI) of ovulatory cycles. Our studies have demonstrated that FLF does not only fundamentally determine female fertility but also has a role in the overall outcome of pregnancy via determining the characteristics of the developing placenta. Mild impairment of FLF (folliculo-luteal insufficiency grade I) is the underlying cause of preterm birth, intrauterine growth retardation and preeclampsia. Moderate impairment of FLF (folliculo-luteal insufficiency grade II) results in miscarriage in the first and second trimester (frequently in an oocyte unable to reproduce), and the most pronounced form (folliculo-luteal insufficiency grade III) leads to inability to conceive and to infertility. Great individual variability of ovulatory cycles is the underlying cause of high complication rates in planned pregnancies of the whole population (38–40%) (miscarriage, preterm birth, IUGR, preeclampsia, etc.). Age-related reduction of childbearing potential (especially over 35 years of age) and the increasingly more common obstetrical complications listed above are also caused by folliculo-luteal insufficiency. Hormonal normalisation of ovulatory cycle disorders also minimises the occurrence of random chromosome disorders mostly of numerical nature. All our statements and conclusions are based on studies performed on a representative patient population and on treatment results.

In our book, we invite the reader to explore this area. We introduce our simple and efficient method for the diagnosis and treatment of habitual abortion and unexplained infertility in a representative patient population. We present our therapeutic procedure called “hormonal wedge resection” implemented for the successful treatment of anovulatory infertility associated with polycystic ovary syndrome. We describe our results that demonstrate the close relationship between FLF and pregnancy outcome. We give an overview on a simple method for the prevention of preterm birth, IUGR, preeclampsia and miscarriages that allows for the reduction of incidence of all human reproductive disorders to less than 10% of the current rate. Regular testing and treatment of preconception FLF can contribute to the birth of healthy generations in the future and would significantly and constantly increase the national annual birth rates (by at least 20–25%). In Hungary, the number of couples failing to have a child is estimated about 150,000. The appropriate care of these couples (by using the efficient, simple and inexpensive methods described herein) can further improve the demographical situation of our country significantly within a few years.

Acknowledgements

Above all, I am deeply thankful to my mentor, Dr. Imre Zoltán (1909–2002), professor, doctor of medicine, the former head of department at the 2nd Department of Obstetrics and Gynaecology at Semmelweis University, the former rector of the Semmelweis University and up to now the only Hungarian vice-president of the International Federation of Gynecology and Obstetrics (FIGO). Seeing my interest in reproductive endocrinology, he extensively supported me.

I owe special thanks to my close colleagues working in the Endocrine Laboratory, Mr. Ferenc Olajos who is the chemical engineer and Mrs. Géza Merényi, Mrs. Dr. Tibor Tóth, Mrs. László Kovács and Mrs. Sarolta Sárközi Nagy who are the laboratory assistants who helped my work to their fullest, and their exceptional diligence and precision were a quintessential necessity for my work.

I am grateful to my friend, Dr. Zoltán Marcsek, PhD in biological sciences, former leader of the United Research Organization of the Semmelweis Medical University and the Hungarian Academy of Science, who provided me devoted, unselfish and versatile help; his irreplaceable help and friendship gave me unique support.

I owe my thanks to every employee of the department, who inspired and helped my work in any way.

List of Abbreviations

ACTH	Adrenocorticotrophic hormone
ACOG	American College of Obstetricians and Gynecologists
APS	Antiphospholipid syndrome
ASRM	American Society of Reproductive Medicine
CBG	Corticoid-binding globulin
CC	Clomiphene citrate
95 % CI	95 %-os confidence interval
CPR	Cumulative pregnancy rate
CRH	Corticotropin-releasing hormone (or CRF)
CRF	Corticotropin-releasing factor (or CRH)
CV	Coefficient of variation
DEX	Dexamethasone
DHEA-S (DS)	Dehydroepiandrosterone sulphate
E1	Oestron
E2	Oestradiol-17 β
ESHRE	European Society of Human Reproduction and Embryology
FLF	Folliculo-luteal function
FLI	Folliculo-luteal insufficiency
FSH	Follicle-stimulating hormone
GnRh	Gonadotropin-releasing hormone
HA	Habitual abortion
HAN	Hyperandrogenism
HPA	Hypothalamus-pituitary-adrenal axis
HPO	Hypothalamus-pituitary-ovary axis
HCG	Human chorionic gonadotropin
HMG	Human menopausal gonadotropin
IR	Insulin resistance
IUI	Intrauterine insemination
IUGR	Intrauterine growth retardation
IVF	In vitro fertilisation
CA	Chromosome abnormality
LH	Luteinising hormone
MPR	Monthly pregnancy rate
NS	Non-significant

P	Progesterone
PCOS	Polycystic ovary syndrome
RCOG	Royal College of Obstetricians and Gynaecologists
RM	Recurrent miscarriage
SD	Standard deviation
SHBG	Sexual steroid-binding globulin (or TEBG)
TEBG	Testosterone-oestradiol-binding globulin (or SHBG)
TTP	Time to pregnancy
UI	Unexplained (idiopathic) infertility

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About the Author



György Siklósi graduated from Semmelweis University with the award “Sub Auspiciis Rei Publicae Popularis” and a gold ring from the president of the Republic of Hungary. Since graduating, he has worked in the 2nd Department of Obstetrics and Gynaecology of the Semmelweis University. He has worked in all departments of the clinic either as a junior physician or the head of department or unit. He was the first deputy director of the clinic for 13 years. He was the head of the first Department of Gynaecological Endocrinology in the country for 15 years. He has been interested in reproductive endocrinology since the beginning of his scientific work. To date, he has published 130

scientific articles in Hungarian and foreign languages and made 150 scientific presentations in Hungarian and at international forums. He achieved a PhD degree in 1986 with his thesis entitled “A nő hyperandrogen állapotai és az azokkal összefüggő reprodukív funkciózavarok” (Hyperandrogenic conditions in women and associated reproductive dysfunctions) and gained a scientific degree of the Hungarian Academy of Sciences in medicine in 1996 by successfully defending his thesis entitled “A luteális funkció meghatározó szerepe az emberi reprodukcióban” (Fundamental role of luteal function in human reproduction). He was among the first individuals to gain habilitation in 1994 in Hungary. He became a university professor in 1997. He was an elected member of the College of Obstetrics and Gynaecology in four cycles and the secretary general of the Hungarian Society of Obstetrics and Gynaecology in two cycles.