Summary

Preterm birth, intrauterine growth retardation (IUGR) and preeclampsia (PE) are probably the greatest challenges in obstetrics at this time. Their causes are basically unknown; thus, their treatment and prevention are unresolved (Muglia and Katz 2010). These three forms of complication account 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 have lifelong effects (Platt 2014). Their significance is further emphasised by the fact that their incidence shows an increasing tendency even in developed countries such as the USA (where the incidence of preterm births increased from 9.4 to 12.5 % between 1981 and 2004). Out of approximately 140 million births every year, 15 million end in preterm birth, 15 million newborns are retarded, there are 7 million cases of preeclampsia and more than 20 million planned clinical pregnancies end in abortion. About 8 million newborns die before the age of 1 every year (Muglia and Katz 2010); 3.1 million of them are solely attributable to preterm birth (Platt 2014). Mortality in retarded babies is 4–8 times higher than in eutrophic newborns (Berkő and Joubert 2009). Preeclampsia still causes 50,000 deaths among mothers worldwide. With the rapid development of neonatology, the survival rate of preterm infants has swiftly increased. However, it has not been able to reduce the lifelong adverse health effects of preterm birth and IUGR, and the number of disabled people has actually increased significantly (Muglia and Katz 2010; Cosmi et al. 2011). Preterm birth significantly increases the incidence of coronary diseases, stroke, type 2 diabetes mellitus, obesity, metabolic syndrome and osteoporosis later in life. It also increases the incidence of insulin resistance, glucose tolerance and hypertension as early as prepubertal age or young adulthood (Barker 2006; Gluckman et al. 2008). Recurrent miscarriage or habitual abortion (5 % of couples), unexplained infertility (5–6 % of couples) and polycystic ovary syndrome (5–15 % of women) are also unresolved problems. Infertility affects about 72 million couples worldwide at any given time (Boivin et al. 2007). Obviously, we can provide a satisfactory 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 our observations regarding the causes of these problems as well as the effective methods for their prevention and treatment.

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According to international scientific societies on human reproduction and the general view of experts, the confirmed presence of ovulation is sufficient for diagnosing a physiological menstrual cycle (ESHRE/ASRM 2012; ASRM 2012/a). The presence and role of luteal insufficiency in human reproduction cannot be demonstrated (ASRM 2012/b). Our methods for the prevention and treatment of human reproductive disorders described in this book 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, thus confirming that ovulation in itself is not enough to declare physiological cycles from the aspect of reproduction. This opened the door for a new, unknown field – the very important field of hormonal insufficiency of ovulatory cycles (folliculo-luteal insufficiency) – in which new relationships can be found that are very important for studying, treating and preventing human reproductive disorders.

During human reproduction, the circumstances of implantation and the characteristics of the developed placenta (size, blood flow, functionality, etc.) are essentially determined by the characteristics of the endometrium, which are in turn determined by hormones produced by the ovaries: the preovulatory oestradiol (E2) and later the luteal progesterone (*P*) and E2 levels. Follicular E2 levels essentially determine the histological features, thickness and blood supply of the proliferative endometrium, the time and value of LH peak and thus ovulation and luteinisation. Folliculogenesis, which is parallel to oocyte development, defines the final karyocytic and cytoplasmic maturation process. After these processes, depending on the preovulatory E2 influence and the *P* levels, the secretory transformation of the endometrium takes place, which eventually determines the conditions of placentation in a direct way (collectively: folliculo-luteal function/FLF). The characteristics of the developing placenta determine the fate of the pregnancy. In physiological circumstances, this process results in the formation of an oocyte and a placenta capable of reproduction and finally in mature birth. But the varying degrees of FLF insufficiency can cause the development of a more or less inadequate placenta and – in more severe cases – the formation of an oocyte incapable of reproduction, thus resulting in an adverse pregnancy outcome.

To clarify the role of FLF in human reproduction, it seemed necessary to determine the characteristics of physiological FLF first. Because of the considerable individual variability in the hormonal levels of fertile women's cycles, we considered a cycle to be definitely physiological if conception took place and was followed by birth. There is a 6-day-long progesterone (*P*) plateau between the 4th and 9th day after ovulation or before menstruation in physiological cycles. As the activity of the corpus luteum is the result of every preceding event in the cycle, we used the value of the 6-day luteal progesterone plateau to quantitatively describe the complete cycle. To reduce the diagnostic error (±49.8 %, 95 % CI) originating from the markedly episodic secretion and the day-to-day variation of *P*, we defined luteal function by the average of three *P* values obtained every other day during the *P* plateau (Siklósi et al. 1984). This way, the physiological luteal *P* value proved to be significantly higher (21.0 ± 2.0 ng/ml) than we previously thought (≥10 ng/ml). After we recognised the strong relationship between FLI and pregnancy outcome,

we modified the *P* value considered as physiological. We deemed a cycle physiological, if conception took place, followed by the birth of a singular, mature and eutrophic newborn ($P = 29.6 \pm 3.3$ ng/ml).

During our studies we observed that the characteristics of the endometrium – and thus placentation also – are determined by FLF, which shows a strong correlation with pregnancy outcome. While we can expect successful pregnancy if the placenta is formed with physiological FLF, folliculo-luteal insufficiency (FLI) gives rise to decreased placental capacity or even the complete failure of placenta formation. Mild insufficiency of folliculo-luteal function (FLI Grade I) is the underlying cause of slight placental impairment (preterm birth, IUGR and preeclampsia). Moderate cases (FLI Grade II) result in more serious impairment (early or late miscarriage), and the most pronounced form (FLI Grade III) leads to the formation of an endometrium inadequate for placentation (infertility). However, these observations can only be verified by successful therapeutic results.

We investigated the effect of FLF normalisation on the pregnancy outcome in a representative, unselected patient population (510 patients, 707 pregnancies) with recurrent miscarriage. Based on the above, we presumed that insufficient placentation is the main cause underlying recurrent miscarriage (RM). The fact that the luteal *P* (13.4 ± 3.3 ng/ml) in RM was significantly ($p < 0.001$) lower than the physiological values (13.4 and 29.6 ng/ml) also supports this hypothesis. Normalising FLF prior to conception with controlled stimulation therapy resulted in a dramatic decrease of the prevalence of abortion as well as preterm birth and IUGR, which occurs 2–4 times more frequently in patients with recurrent miscarriage. The incidence of these complications is ten times lower than in the untreated control group and 5–10 times lower than the national average. The strong correlation ($r = 0.89$, $p < 0.001$) between the average luteal *P* and E2 levels characterising FLF and the length of pregnancy (weeks) and the strong correlation ($r = 0.78–0.90$, $p < 0.001$) between average luteal *P* and neonatal parameters (weight, length, weight percentile, BPD) both confirm our hypothesis. The major determining factor of pregnancy outcome in RM is FLF, which essentially defines the conditions of placental development.

We assumed that in unexplained infertility (normospermia, at least one intact tuboovarian unit and verified ovulation), the underlying cause is FLI of such severity that it causes the formation of an endometrium inappropriate for placenta formation, which is not recognised by the currently available diagnostic methods. This is also supported by the significantly ($p < 0.001$) lower average luteal *P* values (11.3 ng/ml) in UI compared to either the physiological values (29.6 ng/ml) or the values obtained in RM (13.4 ng/ml). By normalising FLF with controlled stimulation treatment, the fertility of patients also normalised. Measured in a representative patient population (621 patients, 838 pregnancies), the monthly pregnancy rate was 29 % on average during the first 3 months, the 12-month average was 26.6 % and the yearly cumulative rate was 98.5 %.

We investigated the relationship between FLF and pregnancy outcome in the treatment of unexplained infertility (625 patients, 884 pregnancies). A significant ($p < 0.001$) difference was found between the average *P* and E2 values of

pregnancies ending in miscarriage, preterm birth and mature birth. We also found significant ($p<0.001$) differences between the average *P* and E2 values measured in the luteal phase of pregnancies ending in the birth of newborns with retardation and of eutrophic newborns. Besides, a strong correlation ($r=0.89$, $p<0.001$) existed between the average luteal *P* and E2 levels that describe FLF and the length of pregnancy (weeks) as well as between FLF and neonatal parameters (newborn weight, length, weight percentile and BPD) ($r=0.78–0.90$, $p<0.001$). In successful pregnancies conceived with physiological FLF ($P>23$ ng/ml), there were no cases with developmental disorders, Down syndrome or other trisomy – including the results of amniocentesis tests ($N=638$). In such pregnancies, the prevalence of preterm birth, IUGR and miscarriage was significantly ($p<0.001$) lower compared to the national average, and preeclampsia did not occur at all. Preterm birth occurred in 0.7 % (national prevalence 9.6 %) and intrauterine foetal growth retardation in 0.7 % (national prevalence 10.1 %). The prevalence of clinical abortion also decreased significantly, to 3.4 % (95 %; CI, 2.3–4.7), while the national average is 15.1 %. These findings clearly suggest that the common cause underlying the aforementioned complications is FLI of varying degree.

Thus, the question arises, what could be the cause of the frequent occurrence of FLI? Our studies have shown that the direct cause of FLI is stress, varying in intensity and time, and/or being overweight, which gives rise to FLI depending on individual reactivity. Continuous low-dosage corticoid treatment (0.5 mg dexamethasone per evening) in FLI significantly ($p<0.001$) improved in FLF. Low-dosage dexamethasone therapy (or if unavailable, methylprednisolone therapy) also proved to be a successful individual and adjuvant treatment for normalising FLF.

Assessing FLF seems inevitable in anovulatory disorders as well. Although in PCOS, which is the most frequent anovulatory disorder occurring in 5–15 % of women, ovulation can be successfully induced in 80 % of patients (with permeable fallopian tubes and normospermia), half of the ovulating patients fail to conceive. According to our studies, FLI underlies this phenomenon as well. We herewith present the therapeutic method called “hormonal wedge resection” we developed to treat PCOS. Using hormonal wedge resection, 97.6 % of patients (120/123) achieved ovulation and (in the case of normospermia and at least intact tuboovarian unit) 98.3 % of ovulating patients became pregnant (118/120), altogether 167 times.

In recent years there has been an increasing trend for couples to put off having children until later in life: the number of women giving birth at over 35 years of age has doubled in the last 20 years. Meanwhile, the prevalence of infertility, miscarriage, preterm birth, IUGR, etc. significantly increases in women who are over 35. During our studies (regarding recurrent miscarriage and infertility), we found that the occurrence of the aforementioned complications in women who are over 35 (between 35 and 45 years) decreased to the same level seen in women who are under 35 years old. At the same time, it was lower by an order of magnitude than the national average. This suggests that it is not the oocyte aging, proportional to

maternal age that underlies these complications, but FLI of varying severity, which occurs more and more often after 35 years of age. Thus, these complications can be successfully prevented with FLF normalisation.

General conclusions can also be drawn from our findings obtained from our representative patient population. Normalising FLF is the most effective treatment for recurrent miscarriage (5 % of couples), unexplained infertility (5–6 % of couples) and PCOS (5–15 % of women). FLF assessment and normalisation is highly recommended before all future pregnancies if the history of the woman in question contains unsuccessful or complicated pregnancy or birth (early or late miscarriage, preterm birth, IUGR, preeclampsia, foetal developmental abnormalities, trisomy, etc.). Regular measurement and normalisation of FLF as part of the preconceptional care would decrease the occurrence of the above complications by an order of magnitude and significantly reduce their severity. But is this just another costly method? On the contrary, the prevention of these complications can be resolved at a fraction of the cost of treating them.

In summary: the increasing occurrence of reproductive disorders as our civilisation goes forward is mainly caused by FLI, which results from stress of varying intensity and duration and/or overweight. The normalisation of FLF with medication before conception allows us to almost fully cure and prevent reproductive disorders (recurrent miscarriage, unexplained infertility) and pregnancy complications (preterm birth, IUGR, developmental abnormalities, etc.). By regularly monitoring and normalising FLF, we may establish the birth of healthy generations and significantly increase the national average number of births per year (at least by 20–25 %). According to estimations, about 150,000 couples in Hungary are currently trying to have a child without success. Their appropriate care (with the presented simple, effective and low-cost methods) would significantly further improve the demographic situation of the country within several years.

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