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Unexplained infertility: 'Leuven' considerations

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I. Fertility: a probability of conception

Fertility and infertility are not all-or-none phenomena, but should be defined in terms of probability of conception.

If it is assumed that the probability of conception remains constant in each cycle, the cumulative pregnancy rates can be calculated (Fig. 1). As can be seen, a probability of conception of 30% per cycle yields a 99% cumulative pregnancy rate within 12 months, while 50% of the women will be pregnant within 1.9 months. If the probability of conception drops to 20, 10, 5 or 2.5% per cycle, the cumulative pregnancy rates within 12 months will be 93, 71, 43 and 22%, respectively, and 50% of the women will be pregnant after 3.2, 6.8, 13.9 and 28 months only.

These calculations are not mere theoretical considerations, but they are extremely important for a correct understanding and management of infertility problems. Since the probability of conception is estimated around 30% per cycle in a normal couple, it is easily understood that one year of unprotected intercourse without a

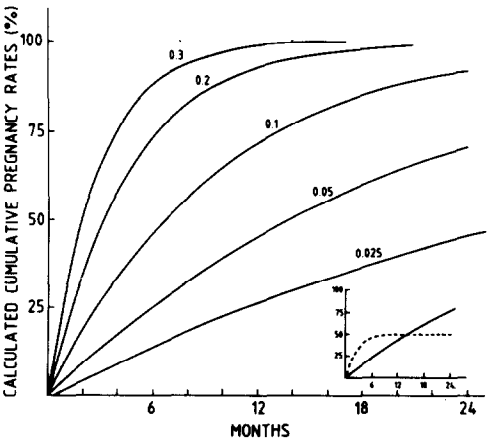

Fig. 1. Calculated cumulative pregnancy rates when the probability of conception per cycle is assumed to remain constant at 0.3, 0.2, 0.1, 0.05 and 0.025, respectively. The inset shows the calculated cumulative rate of a homogeneous population with a probability of conception of 0.05 per cycle (———) and of a heterogeneous population being composed half of infertile couples and half of 'normal' couples with a probability of conception of 0.3 per cycle (- - - -).

pregnancy is considered as infertility, the theoretical cumulative pregnancy rate being 99%. More important, however, are the following consequences. First, if the probability of conception drops below 20% per cycle, the cumulative pregnancy rates after 12 months decrease rapidly. Hence, couples with more than 1 infertility factor will take a relatively long time to conceive. It can indeed be calculated that if the fertility of one partner is lowered by 50%, the cumulative pregnancy rate of the couple will still be 88% within 12 months; if the infertility of both partners is lowered by 50%, however, only 63% of the women will conceive within 12 months. Similarly, a reduction of fertility by 70% in one partner still yields a cumulative pregnancy rate of 75% percent within 12 months; while the same reduction in both partners lowers the cumulative pregnancy rate to 35%. These figures demonstrate that minor problems in one partner, e.g., one ovulation every 2 or 3 months, are relatively unimportant, while the combination of minor problems becomes much more serious.

A second consequence of these theoretical considerations is that neither the effect of a treatment nor a prognosis for the individual patient can be derived from studies in which only pregnancy rates after 6 or 12 months are given. Indeed, (Fig. 1, inset) a 50% pregnancy rate after 12 months can result either from a homogeneous population with a probability of conception around 5% per cycle, or from a heterogeneous population in which half of the couples have a normal fertility (30% probability of conception per cycle), while half of them are totally infertile. The practical consequence is that in the former group the probability of conception during the second year is almost the same as during the first year, while in the latter group the probability of conception during the second year is almost zero.

II. Diagnostic limitations of infertility investigations

Ovulation is generally evaluated by basal body temperature charts, progesterone assays or endometrial biopsy datings. These parameters provide, however, evidence for the presence of a corpus luteum only, not for ovulation stricto sensu, i.e., the release of the oocyte from the follicle. The evaluation of the oviduct by HSG and laparoscopy does not give any information about the integrity of the tubal transport function, which requires smooth muscle contractions, secretion, and ciliary activity. Scanning electron microscopy evaluates the degree of ciliation (Brosens et al., 1976), and even if this could be performed as a routine clinical procedure, the question of representativity of the microbiopsy specimen and of normal ciliary function would still remain. Little is known with certainty about uterine infertility factors: how much intra-uterine adhesion, or how large a submucous myoma or how large a polyp are compatible with a normal implantation and development of the blastocyst? Although it is generally accepted that the development of the endometrium should be 'in phase' with the day of the menstrual cycle, little is known as to why and even if infertility occurs in women with delayed or advanced maturation of the endometrium. Although $20 \cdot 10^6$ spermatozoa/ml are considered as the lower limit for a normal fertility, it is still not exactly understood why so many spermatozoa are needed. Similarly, the qualitative evaluation of the sperm for morphology and motility gives no direct evaluation of the fertilization capacity.

III. Mechanisms which could explain infertility in 'so-called' normal couples

1. Luteal phase insufficiency – the short luteal phase.

Luteal phase insufficiency was initially defined as an endometrial biopsy which is out of phase for more than 2 days on 2 or more occasions (Jones, 1973). Later, it was proposed to make the diagnosis from 1 or 3 subnormal plasma progesterone concentrations taken during the luteal phase (Radwanska et al., 1974). The *short luteal phase* was endocrinologically characterized by low FSH concentrations during the early follicular phase, low 17β-oestradiol concentrations during the late follicular phase and a shortened luteal phase with subnormal progesterone concentrations (Sherman and Korenman, 1974). *Moderate hyperprolactinemia* was claimed to cause luteal insufficiency and/or short luteal phases (Seppala et al., 1976; Mühlenstedt et al., 1978).

The exact mechanism and role of luteal phase insufficiency in infertility has not yet been elucidated. A short luteal phase seems to be triggered by a defective follicular phase (Strott et al., 1970; Sherman et al., 1974; Wilks et al., 1976) possibly caused by a changed bioactivity of LH (Sakai et al., 1980) or a diminished FSH secretion in the early follicular phase. In the Rhesus monkey, the syndrome can be induced by the injection of charcoaled follicular fluid (inhibin?) and thus probably by lowering the FSH secretion (Stouffer et al., 1980).

It has moreover not yet been proven that luteal insufficiency and/or the short luteal phase cause infertility: indeed, proof of repetitivity in successive cycles and absence of this syndrome in fertile women has not yet been established. The success rates obtained with progesterone supplementation (Wenz et al., 1984) and/or clomifene (Downs et al., 1983; Hammond et al., 1982; Quagliarello et al., 1979) suggest, however, that these syndromes do exist as a cause of infertility.

The question of moderate hyperprolactinemia has yielded conflicting reports. Moderate hyperprolactinemia is claimed to induce luteal phase insufficiency, but in women with the latter syndrome, plasma prolactin concentrations are not consistently elevated (Koninckx, 1981). Treatment with bromo-α-ergocryptine is claimed to restore fertility, although prospective randomized trials fail to confirm this. (Michel and Dizerega, 1983) Finally, the diagnosis of moderate hyperprolactinemia is hampered by the frequent occurrence of stress hyperprolactinemia (Koninckx, 1978).

In conclusion, we would retain persistent luteal insufficiency as the diagnosis of a rare (from 3.5 to 12.5% in an infertility population) condition. Although there is no doubt that prolactin affects ovarian function, it is, however, not clear yet whether persistent moderate hyperprolactinemia is a cause of infertility.

2. The LUF syndrome and endometriosis

The LUF (luteinized unruptured follicle) syndrome was described in 1978 as the absence of an ovulation ostium at laparoscopy performed during the luteal phase in women with apparently normal 'ovulatory' cycles (Brosens et al., 1978; Koninckx et al., 1978; Marik and Hulka, 1978). Although its existence was initially questioned, a

laparoscopic evaluation being a subjective and not measurable observation, the steroid hormone concentrations in peritoneal fluid, proved – at least – that the laparoscopic evaluation was not too frequently erroneous. Women with an LUF syndrome have low concentrations of 17β-oestradiol and progesterone in their peritoneal fluid, while these concentrations were much higher in women with an ovulation (Koninckx et al., 1980a, 1980b; Donnez et al., 1983). More recently, the existence of the LUF syndrome was confirmed by ultrasonography (Coulam et al., 1982), and the final proof of the existence of an LUF syndrome was given by demonstrating the presence of an oocyte within the corpus luteum (Koninckx et al., submitted).

The diagnosis of the syndrome can be made by direct inspection of the ovaries at laparoscopy, by ultrasonography, or by assaying 17β-oestradiol and progesterone in the peritoneal fluid. Concentrations of 17β-oestradiol and progesterone higher than 750 pg/ml and 80 ng/ml, respectively, between days 15 and 19 of a 28 day cycle are considered as a proof of ovulation (Koninckx et al., 1980b).

Although nobody will question that a cycle with an LUF is infertile, it is much less clear whether or to what extent the LUF syndrome is a cause of infertility. The only evidence still is the finding that the syndrome occurs statistically more frequently in women with unexplained infertility than in women with explained infertility (Koninckx et al., 1978). Repetitivity of the syndrome in successive cycles is not yet proven, although recently suggested from ultrasonographic observations (Coulam, 1983).

The etiology of the syndrome is still unknown, but the suggestion that stress might be involved, the LUF syndrome being the 'so-called' psychological infertility, was recently supported. Indeed, when evaluated by Spielberger's state-trait anxiety inventory, women with the LUF syndrome were found to have a significantly higher trait anxiety (= are more stress-prone) than women with explained infertility, or than fertile women (Koninckx et al., 1984).

The treatment of the syndrome is unknown, and in our hands neither clomifene, nor gonadotropins, nor bromo-α-ergocryptine will yield impressive results. Prospective clinical trials will indeed be needed before any treatment can be accepted as being superior to no treatment.

Endometriosis has been recognized as a cause of infertility for more than 40 years. The mechanism by which endometriosis causes infertility is easily explained in moderate and severe forms, in which extensive adhesions constitute a mechanical infertility factor, or in which large ovarian cysts impair ovarian function (Brosens et al., 1978). In mild endometriosis, however, the mechanism of the infertility is much less clear. (for review see Muse and Wilson, 1982) Since women with endometriosis very frequently have an LUF syndrome, this syndrome was proposed as being the cause of the infertility (Koninckx et al., 1980c; Schenken et al., 1984). Moreover, it was suggested that endometriosis was the consequence of the LUF syndrome (Koninckx et al., 1980c). Two other mechanisms were recently put forward. First, women with endometriosis have increased numbers of macrophages in their peritoneal fluid and in their oviducts and these macrophages could interfere with fertilization by reducing the number of spermatozoa around the oocyte (Muscato et al., 1982; Haney et al., 1983). Secondly, endometriosis was described as being

associated with increased concentrations of prostaglandins in the peritoneal fluid (Drake et al., 1981; Badawy et al., 1982; Ylikorkala et al., 1984). These data were, however, not confirmed in later reports (Rock et al., 1982; Halme et al., 1983; Sgarlata et al., 1983; Dawood et al., 1984).

Treatment of severe endometriosis is accepted to be essentially surgical. Although several treatments such as clomifene, danazol, pseudopregnancy and/or surgery were proposed in mild endometriosis it has recently been questioned in controlled studies whether pregnancy rates obtained by any of these treatments are superior to those obtained without treatment (Garcia et al., 1977; Guzick et al., 1983; Portuondo et al., 1983; Schenken and Malinak, 1982).

3. Immunologic infertility and subfertile 'normal' semen

In contrast with ovulatory and tubal factors, which can often be considered as all-or-none factors, i.e. ovulation present or absent etc., immunologic factors and semen characteristics should be interpreted as affecting the probability of conception.

Over the last years it has become clear that the presence of sperm-agglutinating or -immobilizing antibodies is not an absolute infertility factor. They reduce, however, the probability of conception and this reduction seems to be proportional to the titers (Fuchs and Alexander, 1983).

Similarly, it is impossible to evaluate exactlly the fertilizing capacity of the sperm. Although a concentration of $20 \cdot 10^6$ spermatozoa/ml was considered as the lower limit of normality, it was demonstrated that the probability of conception by donor insemination was significantly lower in women married to husbands with severe oligospermia (less than $5 \cdot 10^6$ spermatozoa/ml) than in women married to azoospermic husbands (Empaire et al., 1980).

IV. Therapeutic approach to the 'normal' infertile couple

As stressed by Moghissi and Wallach (1983), it is of prime importance that the infertility work-up is done carefully and completely, and that investigations should be repeated whenever necessary. Moreover, it should always be remembered that infertility factors might change as time progresses. Therefore the couples who fail to conceive should be reevaluated after 2–3 years.

We suggest that the factors described as candidates, which could explain infertility in these so-called 'normal' couples, do not cause absolute infertility, but that they lower the probability of conception. Luteal insufficiency, if based on one endometrial biopsy, is a frequent phenomenon and it is easily conceivable that luteal insufficiency is occasionally present in many women. Similarly, an LUF syndrome should necessarily be present in each cycle: if present in only half of the cycles it still constitutes a similar reduction in fertility. Endometriosis, immunologic factors and sperm characteristics could reduce the probability of conception even further. As discussed in section I, the combination of several factors – even of those only intermittently present – will be very harmful to fertility. Since the LUF syndrome seems to be related to stress it can be speculated that male subfertility or sperm-anti-

bodies induce an LUF syndrome in those women who fail to conceive after several months. In these couples, the LUF syndrome will not be the (only) infertility factor, but it would reinforce the infertility by decreasing the already lowered probability of conception.

We therefore feel that before any treatment is started, it is essential to make a guess at the probability of conception per cycle with and without treatment, and that these data be discussed with the couple. This is necessary in order to take into account the fact that, for couples with a rather low probability of conception per cycle, the chances of conception during the first and second and even the third year are the same. This knowledge will decrease the stress in these couples, since they know that their chances per cycle are limited, and it will prevent these women from becoming discouraged when not pregnant after one year. The same considerations hold true when treatment is started. It is a common clinical belief that those women who fail to conceive within 6 months to 1 year of treatment will not get pregnant during that therapy, and for this reason the same treatment is rarely continued for longer periods. This thinking is based upon the unspoken assumption that if a therapy is effective, it should increase the probability of conception to 'normal', i.e. around 30% per cycle. On the other hand, a therapy which, for example, would increase the probability of conception from 5 to 8% per cycle would be an effective treatment, while still only half of the woman would be pregnant within 1 year; moreover, the theoretical considerations developed should dictate that one continue the same treatment, since during the second year again half of the remaining women would become pregnant.

Although these considerations have the advantage of being logical, and seem to be of prime importance for evaluating and planning therapy, data are lacking in the literature. As discussed in section III, 'normal' infertile couples are treated with bromo-α-ergocryptine for moderate hyperprolactinemia, progesterone supplementation for luteal phase insufficiency, danazol for endometriosis, ovulation-inducing agents as clomifene and gonadotropins, or homologous artificial insemination. For all these treatments it can be stated that none of them 'normalizes' the probability of conception. For most of them, on the contrary, only suggestive evidence of a slightly increased probability of conception can be found.

Therefore, instead of discussing the data available in the literature, preliminary results of clomifene treatment in women with unexplained infertility, with minimal endometriosis and with the LUF syndrome will be presented, and these results will be compared to those obtained in women with anovulatory conditions.

V. Results of clomifene treatment in Leuven

1. Materials and methods

Clomifene was given on days 4, 5, 6 and 7 of the cycle, and 15 000 IU of HCG were administered on day 14. Two months of treatment were followed by one therapy-free cycle, and the dose of clomifene was progressively increased every 3 months from 50 to 200 mg per day. The indications for clomifene treatment in these women were amenorrhea, either hypothalamic ($n = 11$) or a Stein-Leventhal disease

($n = 42$), minimal endometriosis ($n = 30$), an LUF ($n = 35$) syndrome, a repetitive short (less than 12 days) luteal phase ($n = 28$) and 'unexplained' infertility ($n = 57$). Cumulative pregnancy rates were calculated for each treatment.

All women treated had an infertility of more than 1 year duration and a complete infertility work-up had been performed in each couple. Tubal function, the uterine cavity and the spermiogram were normal, while the spermagglutinating antibody titer was less than 1/128. Postcoital tests were not taken into account, since they were not always performed repetitively in the immediate preovulatory period.

It would have been ideal to subdivide each treatment group into subgroups in order to evaluate the influence of additional infertility factors, i.e., the effect of minor peritubal adhesions, of suboptimal preovulatory cervical mucus, of a poor postcoital test, of low titers of spermagglutinins and a low normal spermiogram. Since the subgroups were too small to perform meaningful calculations, we only calculated pregnancy rates in a subgroup in which all other infertility factors were considered excellent, i.e., excellent postcoital tests, excellent spermiograms and no spermagglutinins.

2. *Results*

In the whole group of women ($n = 161$) a cumulative pregnancy rate of 30% was obtained after 6 months. The pregnancy rates in successive cycles were 10 and 20%

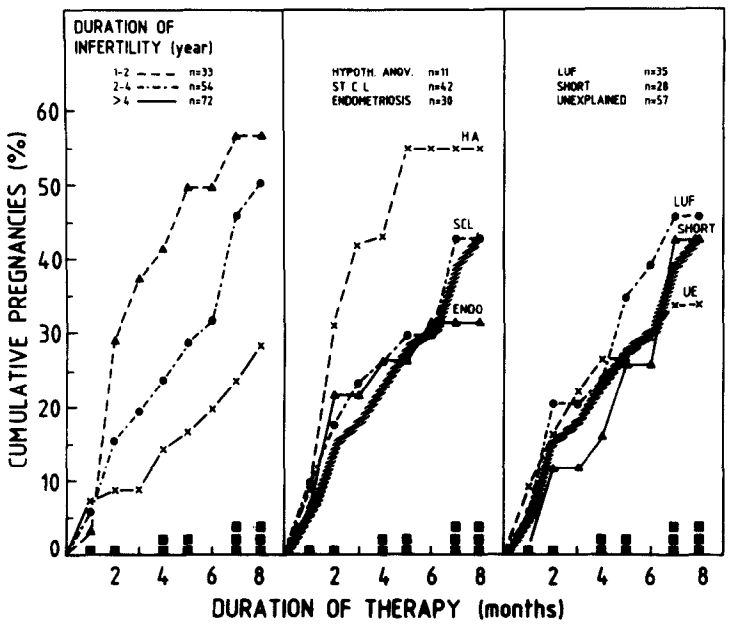

Fig. 2. Cumulative pregnancy rates obtained with clomifene treatment (solid squares on abscissa: 1, 50 mg/day; 2, 100 mg/day; 3, 150 mg/day) in women with hypothalamic amenorrhea, with the Stein-Leventhal syndrome, with unexplained infertility, with the LUF syndrome, with repetitive short luteal phases, and with minimal endometriosis. The hatched area indicates the cumulative pregnancies of all groups together. On the left the effect of the duration of infertility is depicted.

(50 mg clomifene), 8% (untreated cycle), 10 and 11% (100 mg clomifene), and 6% (untreated cycle), respectively.

In women with hypothalamic anovulation a cumulative pregnancy rate of 58% was obtained after 8 months, in women with Stein-Leventhal disease it was 42%, in women with the LUF syndrome 44%, in women with a repetitive short luteal phase 43%, in women with minimal endometriosis 31% and in women with unexplained infertility 33%.

Cumulative pregnancy rates were lower when the infertility lasted for a longer period of time: women with an infertility of 1–2 years, 2–4 years, and more than 4 years achieved cumulative pregnancy rates of 56, 50 and 26%, respectively.

When only couples in which all additional infertility factors were considered excellent were taken into account, cumulative pregnancy rates increased slightly: 64% in women with Stein-Leventhal disease ($n = 14$); 45% in women with an LUF syndrome ($n = 13$), 44% in women with a short luteal phase ($n = 11$), 35% in women with endometriosis ($n = 14$) and 48% in women with unexplained infertility ($n = 23$).

3. Discussion

The most striking result is that the results obtained in anovulatory conditions, LUF syndromes, in short luteal phases, minimal endometriosis and unexplained infertility are very similar. Since it was suggested for minimal endometriosis that no treatment yields the same pregnancy rate as clomifene treatment, the efficacy of clomifene treatment in women with the LUF syndrome, with short luteal phases and unexplained infertility becomes questionable.

The probabilities of conception per cycle in all groups of women treated with clomifene range between 5 and 15% per cycle. We can, however, not yet answer the question as to whether these probabilities of conception per cycle should be considered as a low probability in a homogeneous group of patients or as a combination of higher and lower probabilities in a heterogeneous group. If the former possibility is true, treatment – if effective – should be continued for at least 2–4 years, since we know that only after this period will 90% of the women who ultimately can or will conceive be pregnant. If the latter probability is correct, the duration of treatment can be shorter.

Conception seems to be higher in the second than in the first cycle of treatment. Also in the untreated cycles some women do conceive. Future studies should be designed in order to answer the question of whether the treatment in one cycle influences the fertility in the following cycle.

The data suggest that the probability of conception is lower when the infertility has lasted for a longer period of time. The most likely explanation is that the women with the relatively higher probability of conception conceive quicker than those with a relatively lower probability of conception. The mean probability of conception will thus progressively diminish as time progresses.

Statistical analysis of the data has not yet been performed, since in order to derive meaningful conclusions the treatment groups should be comparable for all infertility factors except the one investigated. If besides age and duration of infertility all other known infertility factors had to be taken into account, the groups would become far too small for statistical evaluation.

We therefore conclude that unless prospective randomized trials are conducted, meaningful conclusions about treatment results can be obtained only with difficulty. From the data presented we would only conclude that the probability of conception diminishes with the duration of infertility. This conclusion could in fact have been anticipated, since infertility is multifactorial. A second conclusion would be that, since the mean probability of conception in all treatment groups can be estimated around 10% per cycle, treatment should at least be continued for several years. But, if this is to be done, it becomes obvious that not only the efficacy of the treatment should be established beyond doubt, but also that no mistakes in diagnosis are made and that the treatment – or combination of treatments – is the best available.

VI. Conclusions

The currently accepted causes of the infertility in the so-called normal infertile couples are discussed, i.e., luteal phase insufficiency, the short luteal phase, moderate hyperprolactinemia, the LUF syndrome, endometriosis, immunologic factors and subfertile normal semen. The available evidence that these factors effectively cause infertility is very limited, but although it can reasonably be accepted that they reduce the probability of conception per cycle, future studies will be necessary to define exactly to what extent the probability of conception is affected by each factor.

The importance of considering fertility as a probability of conception per cycle is emphasized. On theoretical grounds a clearcut distinction should be made between a homogeneous group of women with a low probability of conception per cycle and a heterogeneous group of women composed of normal fertile and absolutely infertile women. Although both groups of women can have the same mean probability of conception per cycle, the outcome is completely different. In the former, the conception rate will remain constant during the first, the second, the third... etc. year, until most women are pregnant. In the latter, 99% of pregnancies will be achieved during the first year and afterwards the probability of conception will become almost zero. These considerations are used to discuss the therapeutic approach: if it can be assumed that the probability of conception per cycle is rather low, therapy should be continued for an appropriate period of time.

Since infertility is so multifactoral, it is stressed that therapeutic results cannot be interpreted unless prospective randomized trials are performed.

In order to substantiate these considerations, the results obtained in Leuven with clomifene are presented. With all the limitations imposed by the design of the study, it can be concluded that the conception rates in women with unexplained infertility, short luteal phase, LUF syndromes and minimal endometriosis are all roughly the same, around 10% per cycle. Future studies will be needed to evaluate (1) the efficacy of clomifene, (2) how long therapy should be continued and (3) the affect of treatment of one cycle on fertility in the following cycle.

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