

ПРОСТАЯ ПРОГРАММА ДЛЯ ПРЕДОТВРАЩЕНИЯ ПРЕЖДЕВРЕМЕННЫХ РОДОВ И НЕКОТОРЫЕ ПРИСКОРБНЫЕ ПРОТИВОРЕЧИЯ

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■ Преждевременные роды и поздние самопроизвольные выкидыши в настоящее время являются огромной проблемой современного акушерства. Важной причиной этих осложнений является восходящая генитальная инфекция, которую можно зачастую предотвратить путем ранней диагностики нарушений вагинальной микрофлоры с применением методики самообследования пациенток. У пациенток с привычными поздними выкидышами или ранними преждевременными родами рекомендуется оперативная тотальная цервикальная окклюзия в качестве наиболее эффективного из существующих методов.

■ **Ключевые слова:** восходящая инфекция; бактериальный вагиноз; профилактика недоношенности; влагалищная pH-метрия; непроходимость шейки матки.

A SIMPLE PROGRAM FOR PREVENTION OF PREMATURE BIRTH, AND SOME REGRETTABLE CONTRADICTIONS

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■ Prematurity and late abortions are still major problems of modern obstetrics. An important cause is ascending genital infection, which can often be prevented by very early diagnosis of vaginal milieu disturbances by the patients themselves. In cases of recurrent late abortions or early preterm births, an operative total cervix occlusion is probably the most effective method currently available.

■ **Key words:** ascending infection; bacterial vaginosis; prematurity prevention; vaginal pH-measurement; early total cervix occlusion.

Introduction

Prematurity, particularly before 32 weeks, is still a major health and financial problem, not only in the field of obstetrics and perinatal medicine, but also for the society as a whole. In Germany, the rate of the extremely early born preterms (< 28+0 weeks) increased from 0.37% in 2001 to 0.61% in 2009 and has remained on this high level since then (Fig. 1) [1, 2]. All very early pretermes (<32+0 weeks) are at high risk for perinatal morbidity and mortality. In Russia in the year 2013, the overall prematurity rate was 7–8%, and the rate of very early born preterms was about 1.5%. But we shouldn't forget about the "late preterms" (34+0–36+6 weeks), which were the majority of all pretermes [personal communication]. The neonatal mortality of "late preterms" is also considerably increased, compared to babies born at term [3, 4]. Similar prematurity rates as in Germany and Russia are found in many other developed countries.

Although many causes of premature birth are known, ascending genital infection is the most important one. The association between bacterial vaginosis and preterm birth is proven [5], but

a problem is that bacterial vaginosis is often asymptomatic. Although in the field of prematurity prevention some promising approaches have been made, from our point of view most of these measures start at an advanced stage of the prematurity process, and the success therefore cannot be optimal. Even in studies, in which screening for and treatment of vaginal infection was performed, the measures often started too late in the pregnancy, therefore successes were inconsistent. Also, in most studies, the screening was performed only once and not regularly [6]. For instance in the study by Kiss et al. [7], with a single screening between 15 and 20 weeks, the number of preterm births in the group of 33+0 through 36+6 weeks was significantly reduced (4.2% in the control group vs. 2.3% in the intervention group). However, the reduction in the groups of very early preterm births and late abortions was not significant. We think the reason is that they also started too late in the pregnancy.

Protective *Lactobacillus* system — a historical and pathophysiological review

The "protective *Lactobacillus* system" and the vaginal pH play a crucial role in the prevention of ascend-

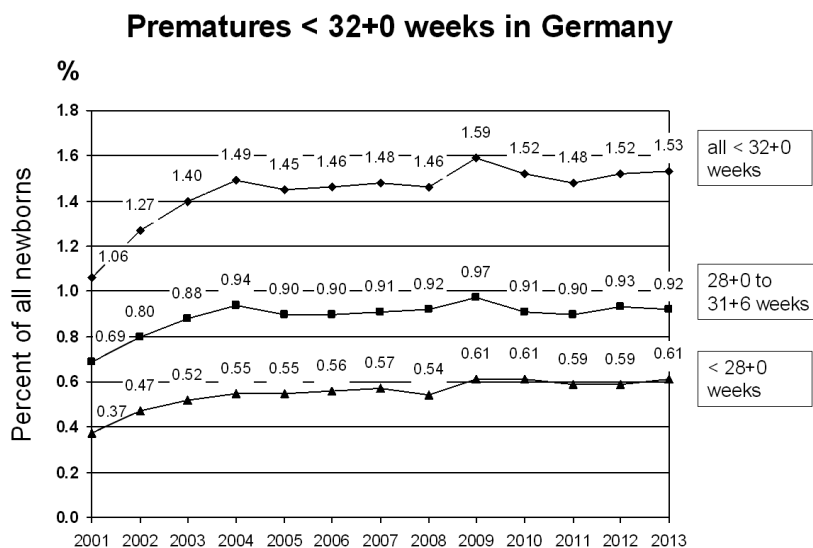


Fig. 1. Rates of very early and extremely early prematures in Germany from 2001 to 2013

ing infections. The importance of *Lactobacilli* for the normal vaginal milieu was first described in 1890 by Albert Döderlein at an international congress in Berlin, and in 1892 written in his well-known book “Das Scheidensekret und seine Bedeutung für das Puerperalfieber” (translated: “The vaginal fluid and its meaning for the puerperal fever”). He made a distinction between normal and pathological vaginal flora, and was the first to use vaginal pH to identify women with pathological vaginal milieu. He also employed lactic acid to restore normal flora and thus to prevent puerperal fever. In order to acknowledge his work, the name “Döderlein flora” was chosen for the normal vaginal flora.

Later Schröder wrote about three different grades of purity (“Reinheitsgrade”), according to Gram’s stain — firstly in 1921 in an article [8], and then in 1926 in a textbook [9]:

- Grade I: Predominantly *Lactobacilli*.
- Grade II: Diminished lactobacillary flora.
- Grade III: Numerous other bacteria with no *Lactobacilli*.

Today we know about many more functions of *Lactobacilli* — these are the main ones: In addition to lactic acid, *Lactobacilli* also produce substances such as hydrogen peroxide, bacteriocins, biosurfactants, and coaggregation-molecules, that inhibit the reproduction and spread of pathogenic germs. However, not every *Lactobacillus* strain produces all these factors. This is the reason why some strains are more effective against vaginal infections than others. Vaginal pH-measurement gives us an insight — like peering through a keyhole — into this protective biosystem (Fig. 2) [after 10].

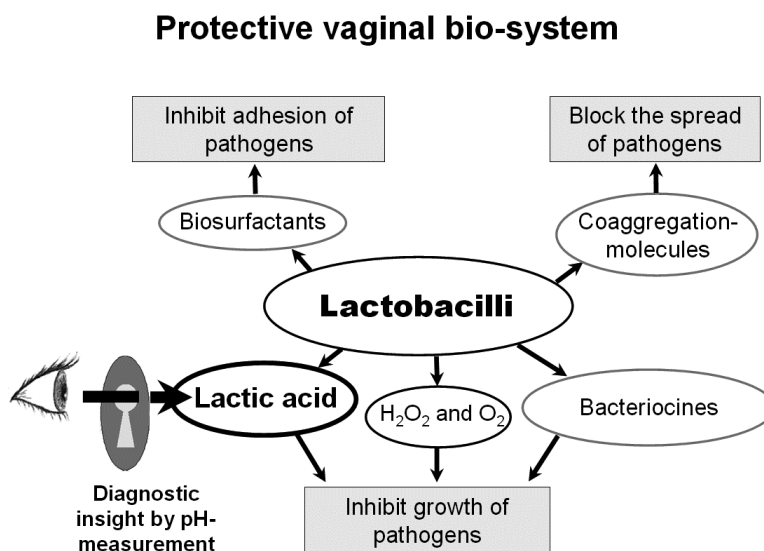


Fig. 2. Functions of *Lactobacilli* and diagnostic insight by pH-measurement

Normal Flora — Disturbed Milieu — Bacterial Vaginosis and other Infections

Bacterial vaginosis and other infections often start with a disturbance of the vaginal milieu, which we consider a “precursor”. Hillier et al. [11] found that in women who in the 2nd trimester had an “intermediate pattern” — between normal flora and bacterial vaginosis — about 1/3 of them developed bacterial vaginosis in the 3rd trimester, whereas 1/3 returned to normal. They consider this intermediate pattern “transitional”. Hay et al. [12] found an increased risk of pregnancy loss in connection with intermediate pattern of vaginal flora and Viehweg et al. [13] reported that even an increase of vaginal pH within the normal range is associated with an increased risk of preterm birth. Donders et al. [14] stated that: “Lactate production, together with peroxidase activity, are believed to be the key factors in the production and maintenance of vaginal acidity and resistance to bacterial intruders.” They also found a good correlation between vaginal lactate concentration and lactobacillary grading in wet mounted specimens. We see these facts as a confirmation of how important vaginal pH-measurement is, because a strong connection exists between pH and lactic acid concentration.

Stages in the preterm birth process

As already mentioned, the ascending infections have precursors. According to Romero, the entire process can last for weeks or even months [15]. It is

most likely that in the cascade of the preterm birth process (Fig. 3)

- the first step is a disturbance of the vaginal milieu. It is essential to take measures at this earliest possible stage, as we do in our program. However, if such early diagnosis and appropriate treatment have been missed, the consequences are often;
- vaginal infections such as bacterial vaginosis;
- an ascension of pathological organisms into the uterus and/or;
- an inflammatory process which can lead to;
- biochemical changes and anatomical consequences at the cervix. To emphasize this again: many measures such as sonographic cervix length measurements or in cases with shortened cervix the application of progesterone respectively analysis of fetal fibronectin are carried out at this advanced stage;
- the next stage is preterm labor and/or premature rupture of membranes and finally;
- preterm birth.

These are events that are often preventable using the simple methods which we recommend.

pH-screening

We therefore think that a probable reason for the success of our Prematurity-Prevention Program — which is described below — is not the early detection of already existing infections, but more the early detection of their precursors. That is a vaginal dysbiosis with decreased number of *Lactobacilli* and an

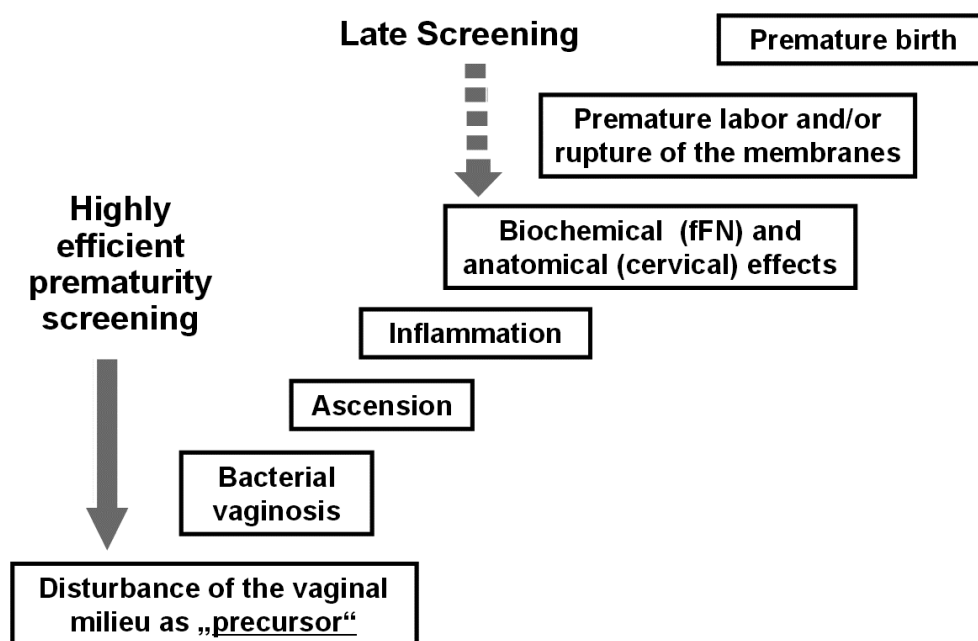


Fig. 3. Cascade of the infectiological prematurity process

elevated pH — but not yet an increase of pathological flora. This is the optimal stage for earliest diagnosis, therapy, and best possible success.

To detect these disturbances, we consider the measurement of the vaginal pH as an easy and efficient screening procedure. According to our investigations in an undisturbed course of pregnancy the pH-value at the introitus vaginae is regarded as normal:

- 4.2 or less when measured with pH-meter;
- 4.4 or less when measured semi-quantitative with the indicator paper that we recommend (art-no. 1.09542 by Merck, Germany) or with the test-glove.

Treatment

When the pH is increased, further diagnostic measures have to follow. The treatment will then be performed according to the situation. Here are just the most common indications:

1. Disturbances of the vaginal milieu (vaginal dysbiosis) without specific signs of bacterial vaginosis or specific infection should be treated locally with hydrogen peroxide-producing *Lactobacillus* preparations for about seven days. We additionally recommend the local application of a lactic acid preparation.
2. Please note that for bacterial vaginosis, we do *not* recommend the sole application of *Lactobacilli*. According to the official guidelines in several countries (also in Germany [16]), bacterial vaginosis should be treated with Metronidazole or Clindamycine. Additional local application of a lactic acid preparation is recommended here, too. An alternative treatment for bacterial vaginosis is the local use of an antiseptic, such as Octenisept® (octenidine hydrochloride + phenoxyethanol). The advantage of antiseptics is, that microorganisms will not become resistant against them.
3. Specific infections should be treated accordingly.

Our Prematurity-Prevention-Program and Self-Care-Measures for Pregnant Women

Since 1989 we have been recommending the *measurement of the vaginal pH* for regular prenatal care by obstetricians [17, 18]. In order to allow the detection of disturbances of the vaginal milieu or vaginal infections much earlier, since 1993 we have been recommending that all pregnant women should regularly measure their vaginal pH twice a week *themselves* from the very start of their pregnancy [19]. With this frequent measurement it has become possible to detect the first disturbances of the vaginal milieu at a much earlier stage and thus to start with therapeutic countermeasures sooner than has ever been possible before.

We have repeatedly published the results of our so-called “Self-Care-Program for Pregnant Women”. Here are some of them: When applying our program, the rate of infants with very low birth weight (<1500 g) was 1.3%, that is six times lower than in the immediate previous pregnancies of the same women, where it had been 7.8%. The rate of infants with extremely low birth weight (<1000g) was 0.9%, as opposed to 3.9% previously [20].

Later Hoyme et al. achieved similar encouraging results with our program in two prospective projects in Thuringia in Germany. In one of them, in the second half of the year 2000 the self-care-program was offered to the pregnant women, and the statistically evaluated results for the entire state were compared with those from the first half of 2000 without the program (in total about 16 000 births). Here the results with regard to gestational weeks: the proportion of very early born infants (<32+0 weeks) was 1.58% in the first half of the year 2000, and 0.99% in the second half. This is a significant reduction of about one third [21].

Regrettable problems in prematurity prevention

Both our own studies as well as the studies performed by Hoyme et al. have some methodological shortcomings. Nonetheless, we think that these studies are important indicators that pH-measurement by the women themselves is an essential step for prematurity prevention. We are aware, that much more research needs to be done. However, it would be inappropriate to neglect the already existing observational studies with their positive results, only because they have not yet been proven by randomized trials.

Unfortunately there are regrettable problems in prevention of premature birth which we already published in the Journal of Perinatal Medicine in 2011 [22]. Let us list only a few of the critical arguments which are partially mentioned already at the beginning of this article:

- It is generally known, that preterm birth leads to many serious problems for the concerned infants, their families, and for the society.
- It is also accepted that most infants and children with cerebral palsy are born preterm.
- It is known that the costs caused by preterm birth are immense.
- The prematurity rates in most countries remain high or are even increasing.
- There are several attempts to prevent preterm birth. Measures often discussed among others are: cervix length measurements, fetal fibronectin and IGFBP-1 findings, and progesterone application. However from our point of view, nearly all of these recommendations are applied under apparently limited conditions (too late within the

often long lasting preterm birth process or too seldom). The recommendation to apply progesterone in all cases of higher risk has the great weakness, that about half of the cases with premature births are in women without identifiable increased risk all cases of higher risk has the great weakness, that about half of the cases with premature births are in cohorts without any identifiable increased risk [23].

- Why do most “experts” accept that the prematurity process proceeds to such an advanced stage until anatomical changes (cervix findings) are detectable by sonographic examinations and in so many of these cases the amniotic cavity has already undergone microbial invasion?
- From the current literature it is known that infection is one of the main causes.
- The frequency of microbial invasion of the amniotic cavity (MIAC) among women presenting with cervical insufficiency is up to 51 % [15].
- Would it not be better to prevent such late stages by using the simple measures earlier, which we described above?
- This, from our point of view, is the reason why no convincing success could be achieved on a broad scale with the help of controversially discussed measures in the literature.
- It seems curious that none of the experts or institutions involved reacted to such a recommended easily applicable low cost program and did not even examine it by their own controlled studies.
- The situation is rather strange as so much advanced research in prenatal medicine is on a surprisingly high level, for instance in the meantime there are approaches to study fetal neurology, and to achieve initial insights into the antenatal backgrounds and origins of cerebral palsy.

In our opinion, this is a seriously regrettable situation caused by self-made preventable faults. But there is a glimmer of hope. The March of Dimes Foundation reacted to our critical comment in the form of a letter to the editor in the *Journal of Perinatal Medicine* and offered support of suitable studies [24]. Unfortunately, up to now nothing happened.

Let us say some words with regard to randomized controlled studies: We are aware that, in times of evidence-based medicine, prospective randomized trials are — or at least seem to be — the “gold standard” when it comes to proving the effectiveness of a given measure. But some physicians raise ethical concerns against randomization. If the method has already shown considerable benefit achieved by observational studies, it is ethically questionable to exclude a considerable number of patients, namely those who are foreseen for the

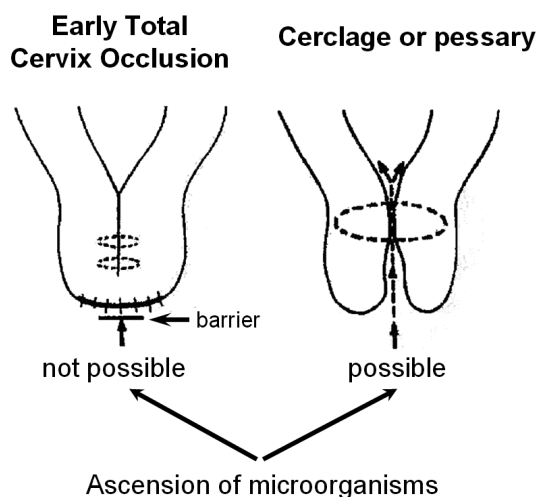


Fig. 4. Early Total Cervix Occlusion versus cerclage or pessary

control group, from the supposedly more effective method. We ourselves did argue in this direction for quite a long time.

Recurrent (2 or more) previous late abortions or early preterm births

The most efficient measure from our point of view for the prevention of ascending infections in cases of recurrent late abortion or early prematurity is to perform an Early Total Cervix Occlusion (ETCO). ETCO creates a total barrier within the cervical canal [25]. This is not to be confused with a cerclage! Fig. 4 shows the main principle differences between cerclage and ETCO. The cerclage (on the right hand), only tightens the cervical canal whereas the ETCO really closes the canal, thus preventing ascension of organisms. In order to allow the lower part of the cervix to grow completely together, the upper surface of the portio — the epithelium — has to be removed completely.

Cerclage is on principle hardly capable of preventing ascending infections because this method only tightens the cervical canal and does not close it completely. Although, theoretically, in a few cases cerclage could support a better retaining of the cervical mucus plug, which plays an important immunological function, but it is hardly possible to predict in which cases this can be expected.

We introduced the ETCO in 1981 as an original early preventive measure for use

- only in women with previous critical history,
- which should be performed early in pregnancy at about 12 weeks, and
- when the cervix is still in an anatomically normal state.

ETCO is now widespread in Germany but is still rarely performed abroad, where for the same indication, usually the cerclage is common. But cerclage

has increasingly become a subject of controversy. The general scientific situation on an international level is rather curious here, because there are no rational reasons for ignoring ETCO. It seems that medicine is sometimes more exposed to fashion trends than to objective science. In the last decades concerning cerclage, several randomized controlled trials as well as meta-analyses have been performed. The conclusion is, that for women with low risk, the cerclage seems not to be indicated, but as regards women at high risk (according to their history), the situation is not quite clear [26, 27].

Noori et al. [28] in addition to a cerclage performed an “external os occlusion suture”. But as they didn’t remove the epithelium, from our point of view, they still performed a very tight cerclage. Nonetheless, they report good results and discussed the concept, that their suture might allow “the build up of mucus plug, thus preventing the ingress of vaginal bacterial flora”. It would be interesting to compare the results of their measure with the results after ETCO in a controlled study.

Our Results with ETCO

To assess the results of ETCO, particularly in comparison to the cerclage, one should only look at high-risk-groups which match the above mentioned indications for an ETCO (≥ 2 late abortions or premature births). We should also consider that the chances of giving birth to a surviving infant are reduced the more late abortions or premature births the woman has previously had.

In 1990, we evaluated retrospectively the data of a group of 113 patients [29] with previous recurrent abortions. From a total of 389 wanted pregnancies only 66 (17%) resulted in a surviving infant.

By the introduction of the Early Total Cervix Occlusion in 102 subsequent pregnancies of the same patients, there were 82 live and surviving infants, this means a success rate of 80%. In 30 pregnancies, only a Late Total Cervix Occlusion was possible. This resulted in 12 surviving infants, which is a success rate of 40%.

Similar good results have been obtained by other clinicians performing the Total Cervix Occlusion: In 1996 we reported the results of a multi-center-investigation [30], in which 11 German hospitals took part and the outcome of a total of 819 pregnancies with TCO was assessed. Particularly interesting are the results among the cases with Early Total Cervix Occlusion. The successes were 85% and without it only 15%. Hormel and Künzel [31] reported similar good results.

Up to now, there are no prospective studies comparing ETCO with cerclage. But in our sample of 113 women treated with ETCO, several women had previously had a cerclage. The benefit was very lim-

ited: In 51 previous pregnancies in which cerclage had been performed, only 13 infants (25%) survived (as compared to a survival rate of 80% with ETCO, mentioned above). These results underline how advisable it is to give ETCO preference over cerclage in cases with such critical history.

Multiple pregnancies

All the results presented up to now concern women who had already had several early premature births, or late abortions in the past. In the meantime more recent results have become available in cases where ETCO was performed as a general preventive measure in multiple pregnancies (which are known to have a higher risk of prematurity), even if the women concerned had not had a poor history.

In 1990, Schulze (from Cottbus, Germany) already started to perform our operative ETCO not only in cases with recurrent miscarriages but also in multiple pregnancies in general. In a publication from 2008 [32] in about 100 cases of multiple pregnancies he showed a significant reduction of preterm births below 32+0 weeks by the performance of the ETCO, even in cases with no other risk factors: The rate was 24.4% in the cases without ETCO and 13.5% in those with ETCO. We are convinced that this is an additional efficient method to reduce the frequency of prematures in multiple pregnancies. The results of Schulze should encourage further studies to verify them from another side.

Final comment concerning ETCO

The Total Cervix Occlusion — in particular the early occlusion (ETCO) is a convincingly efficient measure for the prevention of late abortions and early prematurity

- particularly in cases where such events had previously happened recurrently,
- and also in multiple pregnancies in general.

General conclusion concerning prematurity prevention

We hope this article could give some information, how a considerable amount of premature births could be prevented by the use of the presented relatively simple, inexpensive methods. The overall situation in the field of efficient prematurity prevention is rather curious as so much advanced research in prenatal medicine is on a surprisingly high level. It is in so far unintelligible why applied medicine in its basic requirements is so overdue and so many infants are born much too early and suffer all the critical consequences from their prematurity and, last but not least, the social community loses large amounts of money unnecessarily.

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