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Management of Abnormal Vaginal Flora as a Risk Factor for Preterm Birth

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1. Introduction

Prevention of preterm birth remains a major challenge in obstetrics. While over the years a lot of attention has been given to the structural deficiencies, like uterine abnormalities, or 'weak' or 'insufficient' cervix, during the last decades the importance of ascending infection as a possible cause of preterm birth, preterm rupture of the membranes and intrauterine infection has become increasingly evident (Martius & Eschenbach, 1990). The earlier the preterm labor starts, the higher the likelihood an underlying chorio-amnionitis will be found. While for term deliveries the risk of chorio-amnionitis is around 1%, it is more than 45% in preterm deliveries (Scherman et al., 1997). The damage intrauterine infection causes to the fetus is not limited to the complications and sequels of being born preterm, but also is due to brain damage, like intra- or peri-ventricular hemorrhages and cerebral palsy, caused by the inflammatory reaction due to infection (Romero et al., 2007). Furthermore, such gestational ascending infections may cause maternal complications like sepsis, septic arthritis, maternal respiratory distress (Garland et al., 2002).

Bacterial vaginosis (BV) in pregnancy has an acknowledged increased risk of preterm delivery, but treatment with metronidazole is not beneficial, and if anything, harmful for the pregnancy. Use of broader spectrum antibiotics like clindamycin, or combination antibiotherapy, have shown better results, but still not all studies are in agreement with this. Therefore, critical reappraisal of the prevailing data are crucial, and new studies may need to incorporate new findings and insights. For one, the diagnostic accuracy needs to be refined, as it became increasingly clear that aerobic pathogens and the inflammation caused by aerobic vaginitis (AV), may play a more important role than previously thought. In recent studies meticulously discriminating these differences between BV, AV and mixed AV-BV flora by phase contrast microscopy, it became evident that not only BV may be primarily associated to intrauterine growth restriction and preterm birth, but also the aerobic component may lead to inflammatory reactions in placenta, amniotic fluid and fetus, preterm rupture of the membranes and preterm birth. In this review, emphasis is placed on the most crucial differential diagnostic characteristics, and the treatment adjustments these findings require. Part of this review has been published in the British Journal of Gynecology (Donders et al, 2011).

2. Definition of AV

Diagnosis of AV is based on wet mount microscopy. Normal and abnormal lactobacillary flora are divided into 3 to 4 flora types, also depicted as lactobacillary grades (LBG's). LBG 1 corresponds to a 'healthy' microflora, and has predominant lactobacillary morphotypes of variable size. Lactobacillary grade III is a condition wherein the lactobacillary morphotypes are completely replaced by other bacterial morphotypes. Lactobacillary grade II is an intermediate group, with partial replacement of the lactobacilli by other bacteria. Due to their specific link to pathology, we refined the three grades, and divided grade 2 (LBGII) in a less severe (LBGIIa) and a more severe (LBGIIb) variety (Donders, 1999). As LBG 3, and to a lesser extent LBG IIb are more likely to be linked with pathological conditions, they are entitled 'abnormal vaginal flora'. LBG's are the basis for a composite score to which the following four variables were added: 1) proportional number of leukocytes, 2) presence of toxic leukocytes, 3) presence of parabasal epithelial cells and 4) type of background flora (Donders, 2002). This condition is a screening tool that should not be confused with bacterial vaginosis. Bacterial vaginosis is a condition with abnormal vaginal flora, but abnormal vaginal flora is not always bacterial vaginosis. Some studies demonstrate that the absence of lactobacilli is a more powerful predictor of preterm birth than the presence of bacterial vaginosis (Donders et al., 2008a; Hay et al., 1994). In order to diagnose such abnormal lactobacillary grades, the use of wet mount is preferred above the use of Gram stains due to superior accuracy (Donders et al., 2000c; Donders et al 1996) and better correlation with lactate in the vaginal content (Donders et al., 1998), a functional test for lactobacillary defence function.

Therefore, in this classification, the immune reaction of the host is also taken into account for the diagnosis. Parabasal cells are considered a sign of severe epithelial inflammation usually not seen in uncomplicated BV. They are encountered only in moderate or severe forms of aerobic vaginitis (AV), such as in desquamative inflammatory vaginitis (Newbern et al., 2002; Sobel, 1994). Background flora was allocated score 0 if the background flora was unremarkable or showed debris and bare nuclei from lysed epithelial cells (cytolysis), score 1 if the lactobacillary morphotypes were very coarse or resembled small bacilli (rather than lactobacilli), and 2 if there were prominent cocci, or chained cocci visible. Leukocytes were scored according to their proportional number when compared with epitheliocytes. More than 10 leukocytes per epithelial cell is assigned 2 points, while less than 10 per epithelial cell, but more than 10 per high power field corresponds to 1 point. Adding these points together comprises a composite score, the 'AV'-score. A composite score of 1 to 4 represents normal flora. A score of 5 to 6 to moderate AV, and a score above 6 (to max. 10) to severe AV. In practice, a score of 8 to 10 matches the definition of 'desquamative inflammatory vaginitis'.

The use of this AV criterion enables us to divide the flora in a more detailed and comprehensive way, avoiding undefined and unclear categories. Bacterial flora is lactobacillary type predominant (normal), or it is abnormal. If abnormal the flora can be disturbed by anaerobic overgrowth (BV) or by aerobic micro-organisms, such as *E coli*, group B streptococci, enterococci etc (AV), or can be a mixture of both (mixed AV-BV). Therefore one has to be continuously aware that concomitant infections may occur, and also concurrent infections with *Candida sp.*, *Trichomonas vaginalis*, mycoplasmas or cervicitis (*Chlamydia trachomatis*, *Neisseria gonorrhoeae* and other) (Donders et al., 1993b).

One of the disadvantages of the Nugent score system that is used on Gram stained specimens to diagnose BV (Nugent et al., 1991), is that one does not realize more than one condition may co-occur. In studying wet mounts and applying the BV and AV criteria at the same time, pure BV can be clearly distinguished from pure AV, but at the same time combined forms can be discovered where wherein anaerobic BV flora and AV flora coincide. This mixed AV-BV flora may well be a transient condition between BV and AV, but most likely a prolonged co-infection of both may also occur.

3. Abnormal vaginal flora subtypes in pregnancy

For a few genital infections with severe impact on the outcome of the pregnancy, such as syphilis and gonorrhoea, a 'screen and treat' policy is almost always cost-effective (Donders et al., 1993a; Elliot et al., 1990), while for other infectious conditions, like vaginal overgrowth with mycoplasmas, the jury is still out there to define its precise role in the pathogenesis of infection related preterm birth and fetal injury (Lee et al., 2009; Harada et al., 2008; Carey et al., 1991; Gravett & Eschenbach, 1986).

From the early 90ies it became evident that not only typical pathogens like *C. trachomatis*, *T. vaginalis* and *N. gonorrhoeae* could harm the pregnancy, but also merely aberrations from the normal lactobacilli dominant vaginal flora could endanger the fetus. Although all in the same line, these aberrations were all studied from a different perspective. Most studies used Nugent's or Spiegel's score on Gram stains to detect an association between bacterial vaginosis (BV) and intermediate flora with adverse pregnancy outcome (Hay et al., 1994; Elliot et al., 1990; Lee et al., 2009; Thorp et al., 2008; Cauci et al., 2002c; Hauth et al., 2003; Kekki et al., 2001; Kiss et al., Klebanoff et al., 2005; McDonald et al., 1997; Oakeshott et al., 2004; Verstraelen et al., 2007), but similar findings could be obtained with clinical Amsel criteria to diagnose BV (Honest et al., 2004; Rouse et al., 2009), abnormal lactobacillary grades on both Pap smears, gram stains, and wet mount preparations (Hay et al., 1994; Donders et al., 1993b; Mass et al., 1999; Donders et al., 2009) and with other abnormalities of the bacterial flora than full BV (Donders et al., 2002; Donders et al., E pub ahead of print 2010; Donders et al., 2009).

As is generally acknowledged, Nugent score above 7 on Gram stained specimens corresponds well with BV, and is nowadays accepted as golden standard for the diagnosis of BV in most clinical trials. Compared to this method, wet mount is said to be less sensitive. However, some constraints have to be taken into consideration. First of all, on a continuous scale of 1 to 10, there is no consensus on what the intermediate group with a score of 4 to 6 stands for. If Nugent were an ideal scoring system for bacterial vaginosis, with score 1 to 3 being normal and 7 or above being full blown BV, score 4 to 6 should be transitional, partial or intermediate BV, but in reality it is not. Ideally this intermediate flora state represents a turning point from a normal state into BV, or on the opposite, from BV to normal. However, most of these women with so-called intermediate BV according to Nugent will neither have BV, nor will they become normal. In fact, as they are not having normal flora, nor BV, they rather resemble a sort of 'garbage bin', but this does not mean that they do not represent important pathology. Most intriguing, in almost all studies addressing the importance of BV and the intermediate group as a separate category, it was clear that the intermediate group was linked to a different, and usually more serious scope of complications (e.g. mid trimester pregnancy loss) than the 'classic', full-blown BV (Hay et al., 1994; McDonald et al., 1994).

4. Pathogenesis, immunology and genetics

As AV only rather recently became recognized as an entity that differs in several aspects from BV, lot of its ethiology and pathogenesis remains unraveled. It is not known why the vagina harbours 2 to 3 predominant lactobacillary species (e.g. *L. gasseri*, *L. crispatus*, *L. iners* or *L.*) in normal women (Verstraelen et al., 2009) while in others anaerobes or aerobic commensals overgrow the vagina. It may well be that AV and BV are both ends of the same spectrum of bacterial abnormalities in the vagina, explaining the frequent occurrence of both conditions combined, also in pregnancy (Zodzika et al, 2011). Although it is not clear how the one condition can evolve into the other, it is certainly evident that both conditions express a completely different immunology pattern. Pro-inflammatory cytokines IL1b, IL6 and IL 8 are clearly linked to LBG's in pregnant women, cytokines going up with decreasing numbers of lactobacilli (Donders et al., 2003; Donders et al., 2000a). As was also shown by Cauci et al, BV does express an elevated pro-inflammatory cytokine IL1 b as well, but not the promoter cytokines of the prostaglandin cascade, IL-6 and IL-8 (Cauci et al., 2003), whereas in AV not only IL1b but also dramatic concentrations of IL6 and IL 8 are formed in the vagina (Donders, 2002). As the pro-inflammatory cytokine producers, especially IL-8, in BV women have a different pathogenesis than the (more common) non-producers, and are linked to several risk factors in pregnancy (Cauci et al., 2008; Cauci et al. 2002a, 2002b), likewise the enormous production of prostaglandin provoking cytokines IL 6 and IL 8 in AV patients make them likely candidates for causing preterm labor and delivery (Donders, 2002; Donders, 2007). The links between the presence of vaginal infections, increased levels of IL 6 and IL 8 in both vagina and amniotic fluid and chorio-amnionitis, PPRM and preterm birth are confirmed in several studies (Massaro et al., 2009; Hitti et al., 2001; Rizzo et al., 1996).

5. Prevalence

Prevalence of BV in pregnancy is very variable according to the geographical and socio-demographic area of sampling and ranges from as low as 9% (Larsson et al., 2007) to as high as 48% (Tann et al., 2006). Longitudinal studies show invariably a decrease of BV during pregnancy and a lower likelihood to acquire I with the weeks the gestation progresses (Waters et al., 2008). The prevalence of abnormal aerobic flora or aerobic vaginitis is much more difficult to determine. Besides the prevalence studies on GBS colonization, which ranges between 7 and 25% between 35 and 37 weeks, until recently only sporadic papers have been published on the frequency of AV. Due to the high concentrations of circulating estrogens, severe AV, typically with increased numbers of parabasal cells, is infrequent in pregnancy. However, the prevalence of less extensive types, mild to moderate AV, may range from 8 to 10% according to sporadic studies done during pregnancy (Donders et al., 2009; Zodzika et al., 2011; Rezeberga et al., 2008). Also, it has to be acknowledged that many BV patients have AV to a certain extent as well, - only, the score obtained by Nugent's method will never tell you. Therefore we plea to look for both AV and BV in pregnancy as both conditions are present, need different management approaches and are both linked to adverse pregnancy outcome.

6. Diagnostic techniques and screening

Some authors used aspecific substitute markers instead of Nugent Score for BV detection for exploring risk factors in the vaginal flora during pregnancy. Being one of the crucial criteria

of the Amsel diagnosis of BV, pH is often used as such a surrogate point of care test for BV (Madhivanan et al., 2009). However, in a study where pH was used as a screening tool in pregnancy, only 40% of women with increased vaginal pH had BV (Zodzika et al., 2011). When screening random women in Uganda, we discovered BV in only 27% of women with pH above 4.4 and 39% of women with pH above 4.7 had BV, while another 11% and 25% had coccoid AV respectively (unpublished results). The study demonstrated that AV and mixed AV-BV flora is also a frequent cause of abnormal pH in pregnancy. Hoyme et al. installed a screening in a German state by self measurements of the vaginal pH followed by treatment and found a dramatic reduction of preterm births (<37 gestational weeks at delivery) and early preterm births (<32 weeks) (Hoyme & Saling, 2004). As no specific search for BV was done, the proportion of women treated for other conditions than BV in this study is unknown.

On several occasions, our group could demonstrate that the finding of decreased lactobacillary morphotypes in the beginning of pregnancy is a marker which is strongly linked to preterm birth, even more convincingly so than full BV on its own (Donders et al., 2008a; Donders et al., 1993b; Donders et al., 2009; Madhivanan et al., 2009; Donders et al., 2008b). As is the case with increased pH, also deficient lactobacillary grades are part of the clinical diagnosis of BV, without implying that all abnormal cases necessarily have BV.

7. Outcome

7.1 Miscarriage

Although BV is linked to the increased incidence of spontaneous first and second trimester miscarriage (Hay et al., 1994; Donders et al., 2000b; Larsson et al., 2006; Oakeshott et al., 2002) and reduced baby-take-home-rates in pregnancies obtained through assisted fertility procedures like in vitro fertilization, these data are less clear for AV. In in vitro fertilization procedures, a relation was found between BV and implantation failures (Ralph et al., 1999), but this relation was not confirmed in another observation (Liversedge et al., 1999). Furthermore, amongst these patients a clear relation of BV with tubal infertility was present, (Liversedge et al., 1999; Wilson et al., 2002) indicating indirectly BV is a risk factor for ascending infection and tubal damage. Interestingly, in one study, not BV, but decreased lactobacilli (AVF) was found to be the risk factor of implantation failure at IVF (Eckert et al., 2003). In animals, experiments have shown that *E. coli* derived lipopolysaccharides (LPS) cause implantation failure associated with increased anti-inflammatory cytokines (Deb et al., 2004a, 2004b). No data are available yet about the chances to conceive and keep the pregnancy in women with clinical AV or AV flora, but in sporadic cases pathogenic *E. coli* serotypes were involved in recurrent abortion cases (Blum-Oehler et al., 1997).

7.2 Midtrimester chorioamnionitis

The problem of amniotic fluid infection is that most of the time regular culture techniques are insufficiently sensitive to detect bacterial infection. Therefore, if PCR is used, frequent infection with *E. coli* could be detected amongst these cases even when cultures were negative (Daoud et al., 2008). Also GBS and gram negative rods (Sherman et al., 1997) are frequent causes of intrauterine infections and histologic chorioamnionitis, often leading to midtrimester abortion, and even recurrences in two thirds of the women who have experienced it before.

7.3 Preterm birth

In one study H Mc Donald et al. found an association between midtrimester vaginal colonization with *U urealyticum* and bacterial vaginosis (culture of *G vaginalis*) and preterm birth, but not with enteropathogens such as *E coli* and enterococci (McDonald et al., 1992), but in another study the same authors found such enteropathogens and *S. aureus* to be predictive for preterm birth before 37 and 34 weeks (McDonald et al., 1991). Others have consistently linked colonization of *U urealyticum* or *M hominis* with preterm labor, short cervix, intrauterine infection and preterm birth (Donders et al., E pub ahead of print 2010; Donati et al., 2010; Holst et al., 2006; Hassan et al., 2006). In studies addressing the different subtypes of abnormal vaginal flora, aerobic vaginitis, mixed flora, and partial bacterial vaginosis show a significant relation with preterm birth alongside bacterial vaginosis (Donders et al., E pub ahead of print 2010; Donders et al., 2009; Donati et al., 2010), the latter being more related to growth restriction. After analyzing their studies, Carey and Klebanoff came to the conclusion that rather than just anaerobic BV, overgrowth with *S. aureus* and *E. coli* were the only vaginal bacterial flora linked to preterm birth (Carey et al., 2005). By looking at the microscopic flora patterns as possible risk factors early in pregnancy, we and others came to exactly the same conclusions, namely that aerobic abnormal flora early in pregnancy constitutes a significant risk of preterm labor, chorioamnionitis and funisitis of the newborn (Donders et al., 2008a; Donders et al., 2009; Rezeberga et al., 2008). Our hypothesis is that this link of preterm birth risk with the presence of vaginal flora disturbances associated with overgrowth of aerobic commensal bacteria may be the main reason why treatment with the broader spectrum antibiotic clindamycin is a better approach to reduce preterm birth and preterm rupture of the membranes than metronidazole, which eliminates only the anaerobes (Donders et al., 2009; Larsson et al., 2006; Lamont et al., 2003).

7.4 Intrauterine infection

This would also explain why the pro-inflammatory cytokines that are most closely linked to intrauterine infection and preterm labor, IL 6 and IL 8 are not produced in uncomplicated full BV, but are found in dramatic concentrations in AV (Donders, 2002) and explain the closer association with these cytokines with lactobacillary grades than with anaerobic BV (Donders et al., 2003). In a comprehensive review Roberto Romero and coworkers summarized their voluminous work showing the importance of intrauterine inflammation induced by ascending infection and causing periventricular leucomalacia and cerebral palsy (Romero et al., 2004). Furthermore he and others emphasized the role of genetic variations in polymorphisms creating different responses amongst women to intrauterine infectious challenges (Holst & Garnier, 2008). While it was known since a long time that anaerobic BV associated bacteria can frequently be recovered from the uterine cavity in amniocentesis specimens of women with preterm labor (Martius & Eschenbach, 1990; Hitti et al., 2001; Rizzo et al., 1996; Newton et al., 1997; Krohn et al., 1995; Hillier et al., 1995; Newton, 1993; Gibbs, 1993), most cases of neonatal sepsis are not caused by these BV associated bacteria, but by aerobic bacteria, mainly group B streptococcus, *E. coli* and *S. aureus*. Only recently, for the first time, Rezeberga et al could demonstrate that AV at the first prenatal visit before 12 weeks, detected both clinically as on cultures, was related to an increased risk of chorioamnionitis and funisitis (Rezeberga et al., 2008). Neonatal sepsis, most with *S. aureus*, was also a frequent finding in growth restricted fetuses (Vedmedovska et al., 2010a).

7.5 Intrauterine growth restriction

While women with AV and inflammatory reaction are more likely to develop intrauterine infection, chorioamnionitis, funisitis (Rezeberga et al., 2008) and preterm delivery, the merely non-inflammatory bacterial vaginosis may rather cause growth restriction and preterm delivery of small for date fetuses (Rezeberga et al., 2008). Also in the work of Vedmedovska et al., it was found that genital infections, primarily bacterial vaginosis, was linked to fetal growth restriction (Vedmedovska et al., 2010b).

8. Treatment

8.1 Antibiotics

It is not yet clear which should be the best approach to treat for AV in non-pregnant women, let alone during pregnancy. The inflammatory component of most patients with AV makes one think that antibiotics may not be the best, or not the only approach. But IF is chosen to give antibiotics in pregnancy to reduce preterm birth and intrauterine infection, it became clear after a placebo controlled studies that metronidazole is not the answer as it does not decrease the preterm birth rate in women with bacterial vaginosis (McDonald et al., 1997; McDonald et al., 2007; Carey et al., 2000; Odendaal et al., 2002). Even worse, Klebanoff's (Klebanoff et al., 2001) and Odendaal's study (Odendaal et al., 2002) on the treatment of trichomoniasis and BV, respectively, rather demonstrated an increased risk of preterm birth after treatment with metronidazole, leading several authors to the compelling conclusion that metronidazole should not be used in pregnancy with the purpose to reduce the risk of preterm birth (Donders et al., 2009; Odendaal et al., 2002; Carey et al., 2003; Morency & Bujold, 2007). Investigators using broader spectrum antibiotics, also covering gram positive cocci and E coli, on the other hand, were successful in the reduction of preterm birth in several placebo controlled studies (Larsson et al., 2006; Lamont et al., 2003; Ugwumadu et al., 2003), although not all (Kekki et al., 2001; Kurkinen-Raty et al., 2000; Rosenstein et al., 2000). As most studies used a single treatment course of 5 to 7 days, and test of cure was not always done, one can ask whether a more intensive and repetitive treatment regimen would not be indicated, but studies are lacking.

Use of other antibiotics, aiming at *U urealyticum* and *C trachomatis*, like amoxicillin and erythromycin, have not been successful in the reduction of preterm birth or other infection-related complications in pregnancy (Andrews et al., 2003; Goldenberg et al., 2006; McGregor et al., 1990). Tempera et al tested local kanamycin for patients with AV and performed a detailed analysis of the culture results, proving this may be a successful approach (Tempera et al., 2004). However, even though this antibiotic is not absorbed, tests in pregnancy with this and other similar products have not yet been done yet. Some local, non absorbable with antibiotics, like rifaximin, may have a special promise, due to favorable anti-inflammatory action reducing pro-inflammatory cytokine production as a surplus (Brown et al., 2010). As this has lead to high cure rates in inflammatory bowel diseases such as Crohn's disease, diverticulitis and colitis ulcerosa (Guslandi, 2010; Shafran & Burgunder, 2010; Latella & Scarpignato, 2009), and given the non-absorbable nature, studies exploring the potential of this antibiotic in the treatment of vaginal flora disturbances could be interesting, also in pregnancy.

Finally, also the level of preterm threat may play a crucial role in the efficiency of the BV treatment. Women with BV who have contractions and other symptoms of preterm labor extend their gestation longer when treated for BV than when untreated, whereas asymptomatic women show no difference between treatment versus placebo (Stevens et al, 2004; Briery et al, 2011).

8.2 Antiseptics

Only sporadic and older studies addressed the topic of using antiseptic medication with chlorhexidin, povidine iodine or chloramine as a preventive measure to prevent perinatal and maternal infectious complications in pregnancy, usually without any success (Watanabe et al., 1998; Rouse et al., 1997; Broe et al., 1992). Hence the therapy has been largely abandoned during pregnancy. A recent study shows a beneficial effect of dequalinium chloride vaginal tablets on BV that is comparable to treatment with intravaginal clindamycin, but the effect of this new disinfectant on AV is not known, and studies in pregnancy were not yet performed (Weisenbacher et al., 2011).

8.3 Probiotics

Acidifying or probiotic therapy has also sporadically been tested for women with AVF or BV in pregnancy, but not specifically for AV. In 1990, Holst et al reported a clear benefit of using acidifying cream for BV in a small group of women during pregnancy (Holst & Brandberg, 1990), but this paper was never followed by larger series. A Cochrane review of all randomized trial using probiotics indicated a clear reduction of vaginal infection after the use of oral or vaginal lactobacillus acidophilus containing milk products or yogurt, but data on the outcome of pregnancy were lacking (Othman et al., 2007).

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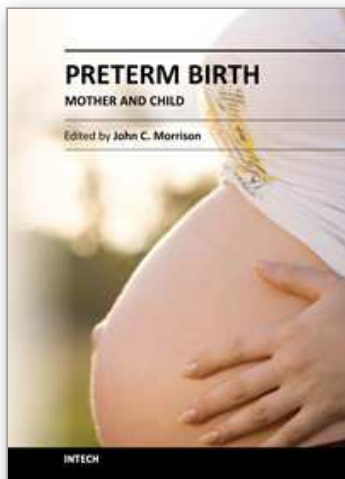
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While there are many studies and books regarding preterm birth, both the obstetric and in the neonatal/pediatric literature, what is missing is the integration of data from obstetrics through neonatal course and into pediatrics as the neonate transverse childhood. A continued dialogue between specialties is essential in the battle against preterm birth in an attempt to relieve the effects or after-effects of preterm birth. For all of our medical advances to date, preterm birth is still all too common, and its ramifications are significant for hospitals, families and society in general.

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