Asymptomatic Bacteriuria during Pregnancy

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Asymptomatic bacteriuria during pregnancy is a rare (2-7%) but potentially hazardous condition which due to what our empirical data dictates us so far, needs to be treated. Yet, regarding neither the laboratory definition nor the therapeutic goals for this 'background' entity for many unfavorable perinatal outcomes (preterm labour, preterm premature rupture of membranes, gestational hypertension, low birth weight, neonatal infections, pyelonephritis), has there been a well structured consensus. This is partly due to our hesitance to try treating with as large a set of antibiotic alternatives as the nonpregnant counterpart but to treat the condition with lower potency and better studied urinary antiseptics, older brand antibiotics and within shortest time intervals hoping to prevent the fetus from getting affected. Not only these special characteristics but also the still lack of many randomized prospective studies questioning the necessity of treating asymptomatic bacteriuria during pregnancy or 'sterilizing the urine', produces a dilemma of whether to use even higher potence medication to eradicate bacteria from the urine at the expense of more side effects, treatment costs and even causing a rebound condition with more resistant strains; or instead make sure bacteria are being suppressed but not necessarily cleansed from the urological tract of the gravid woman, within as short a treatment time as possible with the lowest dosed, cheapest and safest medication, maybe not even antibiotics. We need a better vision about the characteristics of this transient colonization of the lower urogenital tract during pregnancy so as to figure out who is in a more urgent need for treatment or for whom it suffices to manage with an antiseptic only or even no medication at all but natural remedies like probiotics or even cranberry juices.

1. The Definitions

Urinary tract infections are among the most important complications of pregnancy due as well to the physiological changes of the urinary tract during pregnancy.

The changes which predispose the pregnant woman to UTIs (urinary tract infections) include: the relative stasis of the urine in the ureters due to the effects of progesterone, relaxin and the mass effect of the growing uterus which obstruct the ureter at the level of the pelvic inlet, especially on the left side; impaired emptying the bladder and vesicoureteral reflux; increased urine alkaliuresis compensating for the mild respiratory alkalosis of pregnancy. The kidneys are enlarged and the glomerular filtration rate increased by (30-50%) (1).

Bacteriuria is arbitrarily defined as the culture positivity for the same microorganism for at least twice as $>10^5$ CFUs (colony forming units). For pregnant women however, most authors would accept a single culture positivity of $>10^3$ CFUs as significant bacteriuria. (2)

The United States Preventative task force strongly recommends screening for ABU (asymptomatic bacteriuria) at 12-16 weeks of gestation. (3). This strategy identifies 80% of women and monthly screening cultures will only be able to define +(1-2%)/month, thereafter.

Asymptomatic bacteriuria has been identified in 6% of gestations as stated by Kass et al.; 3-7% by Nicolle et al.-2003, and has been found to be associated with prematurity and perinatal mortality.(4,5)

The ABU rate among young healthy women has been reported as 3-5% being more common among diabetics and the elderly.

Vazquez and Abalos further stated that the treatment of this condition with antibiotics was superior to the placebo, diminishing the low birthweight baby delivery rates and the probability of pyelonephritis during pregnancy (6).

2. Etiology and Epidemiology of Asymtomatic Bacteriuria

In pregnant patients, the most commonly isolated uropathogen is Escherichia Coli. Other related microorganisms include other Enterobacteriae (Klebsiella, Enterobacter, Proteus), Staphylococcus Aureus, Staphylococcus Saprophyticus, Enterococcus Faecalis, and group B streptoccocus. (7).

The innate immune system is also very pivotal in the pathogenesis, prognosis and limits of what ABU may progress to be. The Toll-like Receptor system presents a very narrow range of polymorphisms because this system is very crtitical for an intact innate immune system. Whereas, the promoters of this receptor system have a wide range of polymorphisms which have been studied by various authors. Some of these are associated with ABU but protective against APN(acute pyelonephritis)/urosepsis and some, the contrary. Hence, facing such a rich phenotypical mosaic of innate immunity, some bacterial strains (E.Coli 83972) are being used for therapeutical inoculation to colonize and prevent upward colonization by more virulant strains in some clinical situations where the innate immunity is permissive in the lower urinary tract. This is actually a medically set-up symbiotic relation benefiting both the microbial strain and the host. (8)

With regard to antibiotic susceptibility: the ABU/Cytitis-causing and the APN/urosepsis causing E. Coli species were comparable whereas these 2 groups were in sharp contrast considering virulence allelic factors including malX, flmH being more prevalent in the ABU/Cytitis group compared to the APN/urosepsis group. Cnf1 was much less associated with APN an excellent tool even to rule APN. PapG allele 2 was more prevalent in urosepsis and hlyA being very rare. The virulence factors expression of similar E.Coli subspecies isolated from ABU, cystitis, APN and urosepsis (studied with the C. Elegans test) were comparable. Hence, the expression of virulence factors, adhesion properties or microfilm formation are most probably not only dependent on the microrganisms but also on the local immune response and the microenvironment .(9)

3. What if Asymptomatic Bacteriuria during Pregnancy is not treated?

Physicians suggested that 20-40% of asymptomatic bacteriuria during pregnancy if not treated will develop pyelonephritis. (10,11)

As of now, there are no current publications clearly establishing but older ones hypothesizing associations between UTIs and unfavorable pregnancy outcomes (small gestational age babies, preterm deliveries) Banhidy-2010; Mazor-Dray-2009 probably due to advent of more antibiotic prescriptions.(12,13) UTİs, most probably act through prostaglandins to induce labour prematurely (Olson 2003; Romero 1988).(14,15) Symptomatic UTIs have an incidence of 2,3% during pregnancy. APN occurs in %2 of pregnancies and ABU in about 4-5%. APN, even when treated is still further followed by a 40% incidence of ABU and a 23% rate of recurrence; hence the role of ABU following APN for recurrence and the need for prevention of recurrence by treating ABU in these special circumstances. APN is mostly due to E.Coli but also the Proteus, Pseudomonas, Klebsiella and the Enterobacter species. As stated by a recent Cochrane review (conducted by Schneeberger et al.-2012) nitrofurantoin, which has been shown to be an effective antibiotic for the treatment of ABU cannot be effective in preventing recurrent symptomatic UTIs in pregnant patients.(16) What is even more interesting is that nonantibiotic interventions including ingestion of cranberry juices (Japson-2009), known to interfere with the attachment of bacteria to the urinary tract epithelium, lactobacillus supplementation with oral consumption have been shown to be effective in preventing the recurrence of ABU equivalent to daily antibiotic consumption in a study (Beereport-2012).(17,18,19) Treatment of ABU is judged with a lower than threshhold urinary bacterial-culture colony forming units' count but not necessarily a complete sterilization of urine; thus a cure for ABU is actually a diminish in the urinary microbial load; and apparently, does not constitute a total prevention of APN.

Disqualifying the necessity of curing ABU in nonpregnant individuals, there still remains the unanswered question of if and why it still looks necessary to treat it in pregnant individuals. The answers are in fact quite old (Whalley 1967). (19)

In recent years, many controversial ideas have been put forward regarding the necessity to treat this subclinical condition. The debate still continues whether to implement urinary culture as a universal screening test to rule out or define and treat ABU or limit this proposed-to-be preventive measure to only those individuals with risk factors including diabetes, recurrent urinary tract infections or urpogenital tract anomalies. (20).

Gratacos et al. for instance, in a study screening 1652 pregnant women for ABU with a single urinary culture, identified 77 cases of ABU 70 of whom received antibiotherapy and only 7 as the control arm of the study, did not; concluding from pyelonephritis rates of 28% (of the 7 untreated) and 2,8% (of the 70 treated), the authors finally recommended treating ABU to prevent APN during pregnancy.(21)

Smaill et al, 2007 in a cochrane review concluded by pooling data from 4 studies that by treating ABU; contrary to the USPFTF 2004 recommendation, the rate of preterm deliveries were not decreased but only APN was prevented.(22)

Cai et al. inquired the to-treat-or-not-to-treat controversy from a different venture point: the subclinical ABU in women with recurrent urinary tract infections. This study proved that treatment of ABU in nonpregnant young women actually increases the likelihood of recurrent pyelonephritis. This is an interesting finding suggesting that antibiotic therapy is disturbing the microflora of the vagina or the bowel and reducing the colonization resistance.(23) These patients may turn culture negative following antibiotic therapy; however, some of these patients will convert to positive cultures only to show up with multidrug resistant bacterial strains.(23) The antibiotics cause a decreased adherence of the vaginal flora to the vaginal mucosal lining and permit a persistent E. Coli colonization of the vagina.(24) In another good quality controlled clinical trial, antibioterapy has been shown to confer no advantage in young nonpregnant women with ABU, as well (25). So far, we have absolutely no staunch evidence to agree or to disagree with treating ABU in nonpregnant young women. On the other hand, there is at best, an association but not necessarily a morbid effect of poor perinatal outcome in pregnant individuals due to ABU. This coexisting ABU has not been or could not have been cured due to antibacterial resistance, host factors or only suppressed in number as the number of colonies which biase our understanding of ABU in pregnant women.

4. The appropriate treatment duration

Interestingly, conclusions were drawn in a cochrane metaanalysis conducted by Widmer et al. where the effects of different durations of treatment for asymptomatic bacteriuria in pregnancy were assessed. In a pooled data of 1502 cases of 10 different studies within the time period 1982-2009, 772 of which had received a single dose and 730 a 4-7 day treatment; the cure, preterm delivery, the low birth delivery, progression to pyelonephritis, recurrent ABU rates did not pose any significance differences among the two groups. Whereas, only the side effects were significantly more common in the prolonged treatment arm of the analysis. (26)

5. The drug choices: how important?

Krcmery et al. concluded that a single day fosfomycin-trometamol could provide a 95,2% percent cure rate (defined by culture negativity) within a group of UTIs of pregnant women where E. Coli was isolated from about 75-80% of the urinary cultures. These also suggest that long term prophylaxis be applied for recurrent UTIs during pregnancy, those which had to be treated with a long term antibiotherapy, complicated UTIs and in the presence of urinary tract morphological abnormalities.(27)

Ref 12: The antibiotic of choice is the synthetic penicillins and the addition of beta-lactamase inhibitors to these drugs to circumvent the problem of betalactamase positivity of entercoccus. This combination however is not well studied in pregnant patients and the cephalosporins are equally effective alternatives. Nitrofurantoin and fosfomycin have low tissue and high urinary concentrations and good drug alternatives. Quninolones, sulfonamides, nalidixic acid, drugs with high protein affinities are not good alternatives for treating pregnant patients.(28)

(Vazquez et al. 2003) in a cochrane review could not come up with a 'best' choice of antibiotic for the treatment of symptomatic urinary tract infections.(6)

(Guinto et al 2010), again in a cochrane review of 1140 women of 5 different studies, compared different antibiotic choices for treating ABU. Fosfomycin and cefuroxime were similar with respect to persistence, need to shift to another antibiotic and side effects profiles. Pivmecillinam was comparable to ampicillin in all aspects except nausea/vomiting and discontinuing the treatment was more common for pivmecillinam. The 1- and 7-day nitrofurantoin treatments were comparable in all aspects except that persistence of infection was more common for the 1-day regimen. Pivampicillin/pivmecillinam-cephalexin (both category B) and the cycloserine-sulphadimidine (categories C and D,respectively) comparisons did not show any significant differences, either. (28)

First line antibiotic choices on the other hand, differ in different countries: Beta-lactams and nitrofurantoin in Denmark, Sweden and Norway; amoxycillin in the USA; trimethoprim and nitrofurantoin, in Canada; and penicillins/cephalosporins, in the UK.

Czaja et al. (2007) sums up the antibiotic choices as: (29)

1. Sulfizoxazole 500mg by mouth 3 times daily for 3-7 days.
2. Amoxicillin 500mg by mouth 3 times daily for 3-7 days.
3. Amoxicillin/Clavulanate 500mg by mouth 2 times daily for 3-7 days.
4. Nitrofurantoin 50mg by mouth 4times daily for 3-7 days.
5. Cephpodoxime proxetil 100mg twice daily for 3-7 days.
6. Fosfomycin 3gm by mouth as a single dose.

6. Finally

As of now, there have been 4 main meta-analysis conducted about treating asymptomatic bacteriuria:

1. Villar et al., 2000: compared different durations of treatment for asymptomatic bacteriuria, concluding with no net difference among different durations of treatment except the longer intervals causing side effects more commonly.
2. Vazquez et al., 2003: sets an analysis to question the most effective antibiotic choice but only for symptomatic urinary tract infections during pregnancy, concluding that there does not exist any best or most effective set of drugs.
3. Smaill et al., 2007: questioned whether to treat or not treat the condition concluding that treatment prevented APN and SGA deliveries but not necessarily preterm deliveries.
4. Guinto et al., 2010: asked the same question as in item 2 about treating ABU during pregnancy, similarly unable to find any specific first choice antibiotic therapy.

As a general conclusion, ABU is most probably a commensal relationship between the host and some bacteria, and at the time a necessary but not a sufficent background factor in the pathogenesis of symptomatic or higher urinary tract infections. It may be a cause or an associated factor to some unfavorable perinatal outcomes including preeclamsia, low birth weight deliveries which remains to be further analysed. So far, it appears better to intervene with ABU during pregnancy than not. The term 'cure'; however, has to be pinched out because both the measures of diagnosis and

treatment are arbitrary. Leveling up in antibiotic choices, treatment durations interestingly do not translate into better treatment results. Hence, we are supposed to consider our treatment goals as suppression but not necessarily cure. The medical intervention should be with the drug of the least side effects for both the baby and the mother; the most effective cost and the shortest ingestion interval.

It would be very interesting to define the postpartum prognosis of ABU; to question the necessity of a control culture following the treatment of ABU to diagnose recolonizations during and after pregnancy.

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