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# Are we using too many antibiotics during pregnancy? A Commentary

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American physicians prescribe too many antibiotics for the pregnant woman and the fetus in utero. Practice modifications in 1996 and revised in 2002 to prevent Group B Streptococcus (GBS) infections in newborns[1], and in 2010 to reduce the incidence of postpartum maternal infection after cesarean section[2] have led to the use of pre-delivery antibiotics in ≥ 40% of women in labor (and to the fetus). Prior to 1996, few of these children in utero would have been exposed to antibiotics. These obstetrical strategies stand in contrast to concerns about overuse of antibiotics in children, and run counter to the CDC campaign that has reduced children's antibiotic prescription rates for office-related visits by 24%.[3] Should these increases in antibiotic prescribing by obstetricians be a concern? We think so.

The immediate impact of these two strategies has been favorable. The incidence of disease due to GBS in the newborn is reduced when pre-delivery antibiotics are administered[1], and the frequency and severity of infection in post-cesarean delivery mothers is also reduced,[4] with few immediate complications. Maternal allergic reaction to these prophylactic antibiotics is rare, and the development of resistant bacterial infections in either mothers or newborns has not as yet been a focus in the literature.

A belief in the long-term safety of pre-delivery antibiotics has been maintained in part, because meaningful prospective statistics are not being collected. In the current reality of early discharge from the hospital, many mothers with post-partum infection have their first symptoms at home. When seen most often by a doctor in their office, a draining abdominal wound is labeled a "seroma" and the woman treated with oral antibiotics without a culture. Since most women get better with this approach, only the uncommon woman with treatment failure requires hospitalization. Long-term changes in bacteria causing post-operative infections will not be easily detected with this practice pattern.

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A similar sense of the universal effectiveness of predelivery antibiotics for the fetus is undeserved. In most community hospitals, very low birth-weight babies are transferred to testing centers where their care is not observed by the transferring physician. Outcomes are not always apparent. At least two studies have shown an increase in *Escherichiae coli* sepsis in very low-birthweight newborns, whose mothers received antibiotics to prevent newborn GBS infection.[5] This trend has not been reported in term babies.

There are other potential concerns about pre-delivery use of antibiotics. Pre-delivery antibiotics affect the bacterial populations of the mother's birth canal and skin, which will be transmitted to the babies during and following delivery. Changes in the composition of the indigenous microbiota of newborns have the potential to influence childhood development and disease risk. The rapid increase in recent years of illnesses with onset in childhood (including asthma, type 1 diabetes, obesity, and autism) suggests an environmental cause could be present. The loss of one or more constituents of the indigenous microbiota after maternal antibiotic exposure could be a contributing factor[6]; this hypothesis should be studied.

Changes in early life microbiota of children may matter. (For example, the loss of *Helicobacter pylori*, disappearing from the gastric microbiota in mice, has resulted in decreases in gastric T-cell populations.[7]) This change provides a basis for the increases now being seen in childhood asthma, allergic rhinitis, and skin allergies.[6] Currently, few young children have *H. pylori*–mediated regulation of gastric adipokines, such as ghrelin and leptin[8] at a time in life when long-term adiposity is being programmed; *H. pylori* removal increases post-prandial ghrelin levels.[8]

In another example, farmers add antibiotics to the food and water of young animals for "growth promotion." In that setting, antibiotics are changing early life metabolism; is this an analogue for how we are treating our children and their mothers just before birth? A recent study by Cho et al. showed that subtherapeutic antibiotic therapy to young mice increases adiposity.[9] There were substantial taxonomic changes in the microbiome, changes in copies of genes involved in the metabolism of carbohydrates to short-chain fatty acids (SCFA), increases in colonic SCFA levels and alterations in the regulation of the hepatic metabolism of lipids and cholesterol. Clearly, antibiotic use in farm animals for growth, now banned in the United States, involved long-term use of low-dosage antibiotics. Pre-delivery antibiotics are short-term, but are given at a critical time when newborn acquisition of gut bacteria is just beginning. With the current (and growing) use of antibiotics affecting early life development, are we spawning a population of children at risk of being less healthy than prior generations? These issues should trigger discussion about current guidelines for care of pregnant women. What can we do?

One approach would be to develop safe strategies that limit the use of antibiotics in women in labor. In the pre-guideline era, Group B sepsis in the highest risk newborn population (very small prematures) occurred in 5.9 cases per 1,000 population.[1] To protect one small premature child from GBS infection, over 100 others are exposed to antibiotics.[1] It also is clear that risk of infection differs. For example, the incidence of GBS infection in the newborn is greater in women who have previously delivered an infant with a GBS infection,

have a history of first trimester GBS bacteriuria, are delivering a premature (< 37-week) baby, have prolonged (> 18 hours) rupture of membranes, and/or are African-American[1], compared to women with uncomplicated pregnancies delivering at term. Also, whether or not GBS is present in vaginal or intestinal tract, women who undergo elective cesarean section who are not in labor, and whose membranes are intact are at very low risk, and antibiotic prophylaxis had not been recommended for this group[1]. Instead, it is now recommended in the United States to prevent postpartum maternal infection[2], and in consequence is now always being given.

For women at term with a positive GBS culture at 35–37 weeks, alternatives to maternal antibiotics should be considered. Although not adequately studied, a dilute hexachlorophene vaginal douche at the time of admission for labor is one alternative, but this strategy is flawed, for it still affects birth canal microbiota. A possibly more appealing strategy is the performance of a rapid (PCR) testing for Group B *Streptococcus* presence at the time of admission to the labor and delivery unit. A negative PCR would eliminate antibiotics for women in premature labor and those women who were culture-positive at 35–37 weeks, who had cleared the bacterium. The fact that the PCR assay currently takes from one to two hours would eliminate its use in women in active labor expected to deliver in less than six hours, but it would eliminate the use of antibiotics for some patients. Further technologic research is needed to improve the speed of this assay while maintaining sensitivity. A more satisfying approach would be the development of a vaccine to promote the elimination of the Group B streptococcal carrier state in the mother. This is currently under investigation.

The concept of a single policy for giving antibiotics before cesarean-section should be questioned, since the risk for post-operative maternal infection varies widely.[2] The lowest-risk group consists of women undergoing cesarean section with membranes intact, who are not in labor. Although a large (9,432 women) observational study showed that prophylactic antibiotics, with statistical significance, reduced risk of post-operative infection,[10] what is the clinical significance? The strategy of employing prophylactic antibiotics in this population means that 1,000 women receive antibiotics to prevent six cases of endometritis and 4.4 cases of abdominal wound infection.[16] About one hundred mothers and their babies are exposed to antibiotics to prevent each maternal infection. A group with even lower-risk could be identified by using the index-scoring method of the American College of Surgeons in which maternal risk factors can add two points to the score.[11] (Table 1) A pregnant woman with a score of 0 could safely forego prophylactic antibiotics. The highest-risk group of women undergoing cesarean section consists of those in labor with ruptured membranes with risk index scores of 1 or 2. To date, the best reported approach to prophylaxis in this high-risk population has been a combination of two antibiotics given after cord clamping, which eliminates fetal exposure to the antibiotics.[12] Such alternative approaches are examples that would reduce use of pre-delivery antibiotics, with minimal adverse impact upon mothers and newborns.

In summary, in our well-intended zeal to reduce infectious complications of delivery, we may have (paradoxically) impacted the microbial milieu for the next generation of newborns. The growing concern about long-term consequences of early life exposures to antibiotics requires contemplation of new strategies for risk stratification of pregnant women

and new approaches deployed. Long-term studies of current newborns need to be implemented so that the magnitude of the problem can be documented.

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**Table 1**

Risk index scoring system for postoperative infection[11]

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|---|
| A patient with an American Society of Anesthesiologists preoperative assessment score of 3, 4, or 5. |
| An operation classified as contaminated or dirty infected. [Does not apply to most obstetric patients.] |
| Operations lasting over *T* hours: for caesarean delivery *T* = 1 (where *T* is the accepted length of time for an uncomplicated caesarean delivery). |