FEBRUARY 2019

PAEDIATRIC INFORMATIONSERVICE

The intestinal microbiota – An important key to health: The impact of delivery type and other influencing factors on early childhood development

By Dr. Bettina Dörr

Knowledge of the composition and health implications of gut flora (also called intestinal microbiota), as well as what influences it, is growing at an unprecedented rate. In the coming years, paediatricians can expect to read plenty of interesting scientific literature on this topic. The foundation for a person's microbiota is laid by the mother and is influenced both by the conditions inside the womb as well as by the delivery type and the subsequent diet and lifestyle.

This article summarises current knowledge on the development of a newborn's microbiota. It focuses on influencing factors such as the type of delivery (caesarean), use of medication and the composition of the infant's diet.

The data produced in recent years confirms the impact of these factors on the microbiota and subsequently on the risk of disease in later life.

Strategies on how to influence the microbiota in infants born by C-section

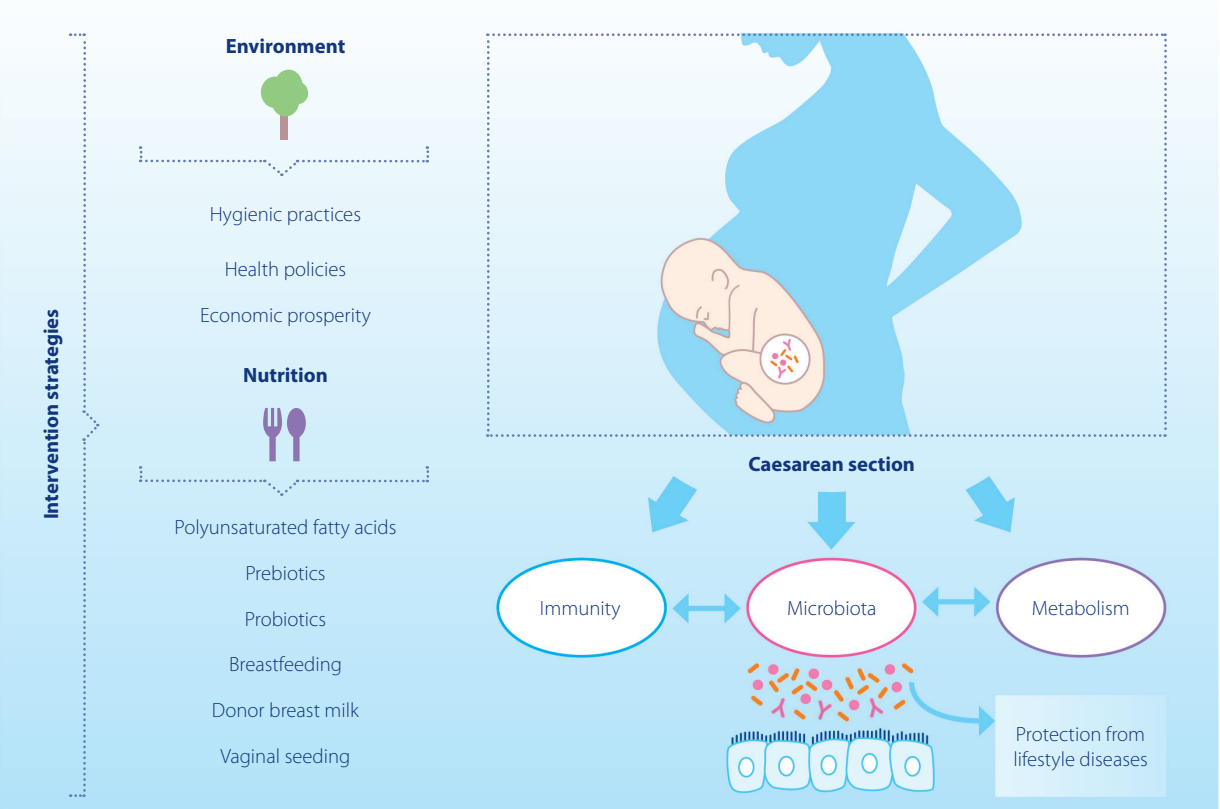

Fig. 1: *Modified based on Moya-Pérez A et al. 2017*

C-section: increasingly popular, but with significant consequences

The circumstances under which a baby is born directly influence the infantile microbiota and thus lay an important foundation for both the early stages of life as well as later life. In comparison to vaginally born children, infants born by C-section are 30 to 50 per cent more likely to develop diseases such as allergies, asthma, type 1 diabetes, and other autoimmune diseases. Current studies also suggest a link between the occurrence of neuropsychiatric disorders such as autism and ADHD (attention deficit hyperactivity disorder) and an altered microbiota (**Fig. 1**, Moya-Pérez A et al. 2017; Felice VD and O'Mahony SM 2017).

According to the recent statement of the German Society of Paediatrics and Adolescent Medicine, about 30 per cent of German children are born via C-section. This makes the C-section the most frequently applied obstetric intervention and, compared to vaginal births, it entails an approximately five times higher risk of postpartum infectious complications. Therefore, current guidelines recommend a perioperative antibiotic prophylaxis, which can be administered after the umbilical cord has been clamped or just before the incision. However, this measure means that, every year, more than 200,000 children already receive antibiotics via their mother at birth. The question of whether administering prophylactic antibiotics to the mother prior to the C-section incision has any disadvantages for the neonate cannot be answered conclusively due to lack of reliable data (Deutsche Akademie für Kinder- und Jugendmedizin e. V. and Huppertz 2018). What is certain, however, is that there is a link between exposure to antibiotics during early childhood, the composition of the microbiota and the development of atopic diseases.

An infant's microbiota is impacted not only by the antibiotics administered during C-section but also by the lack of oral and cutaneous contact with the maternal vaginal and rectal flora. The microbiota of infants born via C-section predominantly constitutes germs from the hospital environment as well as maternal skin bacteria, while important lactobacilli and Bacteroides are significantly reduced. These alterations of the microbiota and the delayed bacterial colonisation, when compared to vaginally delivered infants, are the basis for the discussion of the increased occurrence of diseases in later life. Another interesting aspect is the fact that the delivery type not only influences the microbiota but also the colostrum. An Italian research team was able to show that the first breast milk of mothers who had delivered vaginally contained significantly less Pseudomonas, staphylococci and Prevotella than that of mothers who had had a C-section (Toscano M et al. 2017).

The different composition of the microbiota, depending on the different delivery types, is particularly visible in the first three months of life (Rutayisire E et al. 2016). However, according to some of the available data, differences can still be detected after seven years. A study of 7-year-old children, for example, found a significant difference in the clostridia count (Salminen S et al. 2004).

Drugs that influence the microbiome

New studies have shown that antibiotics are not the only drugs that can affect the microbiome, and that drugs like gastric acid inhibitors, which are sometimes given to babies with reflux, can also have an altering effect. Infants who received antacids and antibiotics during the first six months suffered significantly more often from allergic diseases such as food allergies, asthma, neurodermatitis, hay fever (allergic rhinitis), contact dermatitis and drug allergies. This was also the conclusion drawn by a retrospective cohort study, which was published in JAMA Pediatrics (Mitre E et al. 2018).

First contact with bacteria already inside the womb?!

Besides the gut microbiota, scientists are currently also investigating the endometrial microbiota (Moreno I and Franasiak JM 2017). There is growing evidence to suggest that the womb is not a sterile environment, but rather contains a special bacterial spectrum. Due to the detection of bacteria in the amniotic fluid and the placenta, it is possible that the development of the infantile microbiota starts long before birth and is therefore highly influenced by the environment in the maternal womb (Chong CYL et al. 2018; Dunn AB et al. 2017). How the bacteria enter the amniotic sac during pregnancy is not yet fully understood.

There are two main pathways that are currently being considered: vertical ascension from the vagina and/or urinary tract and a haematogenous route through translocation from the digestive tract (**Fig. 2**, Milani C et al. 2017). Conclusive results of other studies still have to be presented, as the theory of a

Possible ways in which the maternal microbiota is transferred to the infant

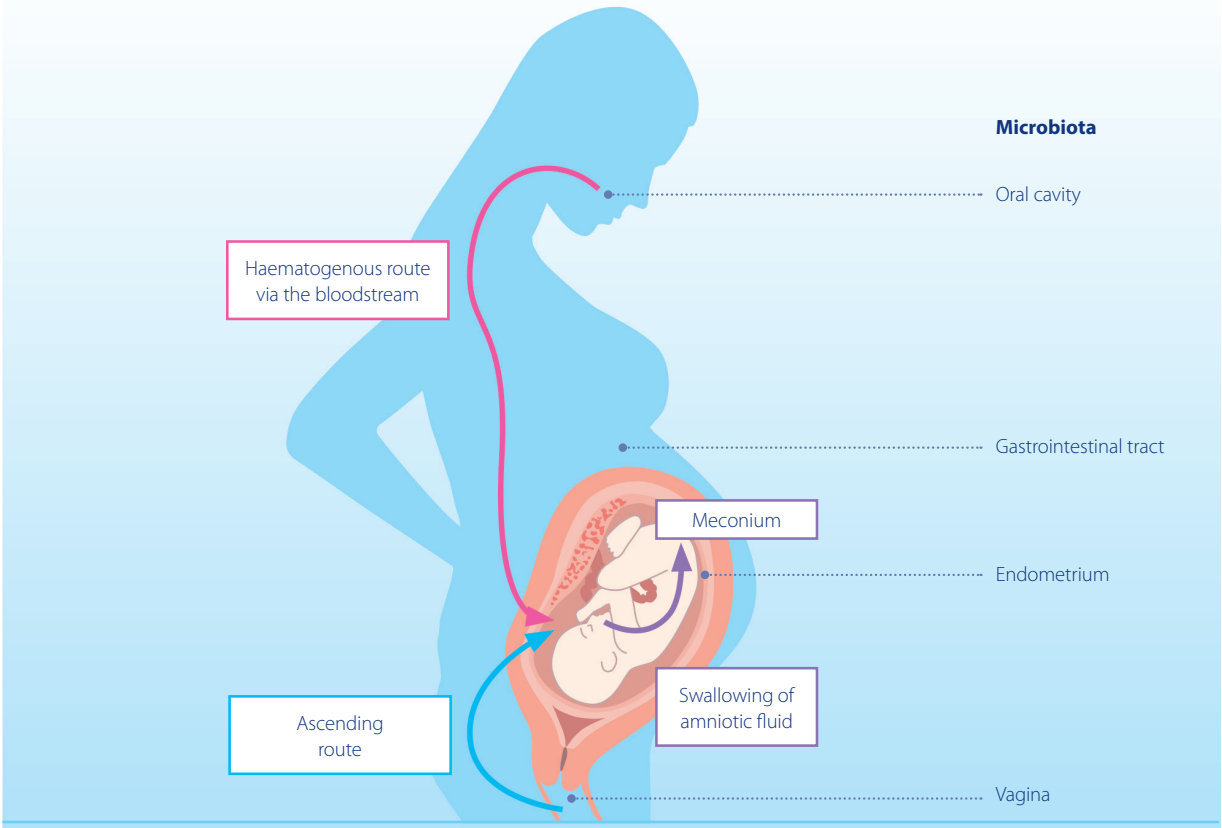

Fig. 2: *Modified based on Milani C et al. 2017*

microbial colonisation of the uterus is currently still being discussed (Willyard C 2018).

Vaginal seeding – the solution for caesarean sections?!

Vaginal seeding, which describes the procedure of microbial inoculation of the neonate with missing "healthy" germs by swabbing the oral cavity, face and body of the infant with maternal vaginal fluids immediately after C-section, is still a subject of controversy. Recent statements from the ACOG (American College of Obstetricians and Gynecologists), as well as the Danish society DSOG (Danish Society of Obstetrics and Gynaecology), suggest that this practice, which strives to emulate the natural situation in which maternal fluids containing vaginal flora are transferred onto the neonate when they pass through the birth canal, cannot yet be recommended as routine procedure. The respective societies have not yet been presented with sufficient clinical studies and they have raised concerns that a possible infection of the mother with streptococci and/or viruses or chlamydia could be harmful to the neonate (ACOG 2017; Lee LY et al. 2017; Haar T et al. 2018).

Advocates, however, rebut this argument by pointing out that this risk is equally present in vaginal births and can be minimised through corresponding laboratory analyses.

Recommendations extracted from what is known today therefore suggest that the advantages and disadvantages be weighed up together with midwives and gynaecologists. This way, the use of this method can be discussed based on the individual health status of the mother.

Both the targeted use of safe and appropriate probiotic bacteria in infant formula as well as the maternal ingestion of probiotics is presented as an alternative by some experts (Stinson LF et al. 2018).

Nutrients can do more than just nourish – this is also valid for microbiota

The type of delivery is not the only key factor for a well-balanced and diverse microbial colonisation; the subsequent diet is also decisive. Breast milk remains the best foundation for an infant's development. It not only contains all the common nutrients for healthy growth and development, but also pre- and probiotics, which are necessary for the healthy development of the microbiota. During breastfeeding, good bacteria (probiotics) as well as special carbohydrates (prebiotics), which can be seen as "food" for the bacteria, are passed on to the infant (Cabrera-Rubio R et al. 2016). The prebiotics contained in breast milk are called human milk oligosaccharides (HMOs). Other known prebiotic substances are, for instance, galacto-oligosaccharides (GOS). All of these special carbohydrates are characterised by the fact that they cannot be metabolised by human digestive enzymes, but only by intestinal bacteria.

These special carbohydrates are now summarised under the term microbiota-accessible carbohydrates (MACs).

Health-promoting intestinal microbes such as lactobacilli and bifidobacteria use MACs as a nutrient source. This way they can propagate and release substances which in turn are useful to the human body. These substances include short chain fatty acids (SCFAs), which are essential for a healthy intestinal mucosa, but also have a general beneficial effect on the human body as they enter into the bloodstream and are distributed throughout the body, see also **Fig. 3** (modified based on Sonnenburg ED and Sonnenburg JL 2014). The combination of health-promoting bacteria such as lactobacilli or bifidobacteria and prebiotics is summarised under the term "synbiotics". For the development and maintenance of a healthy microbiota, both nutrients are essential. This is valid for both mothers as well as neonates.

Schematic structure of MACs such as GOS

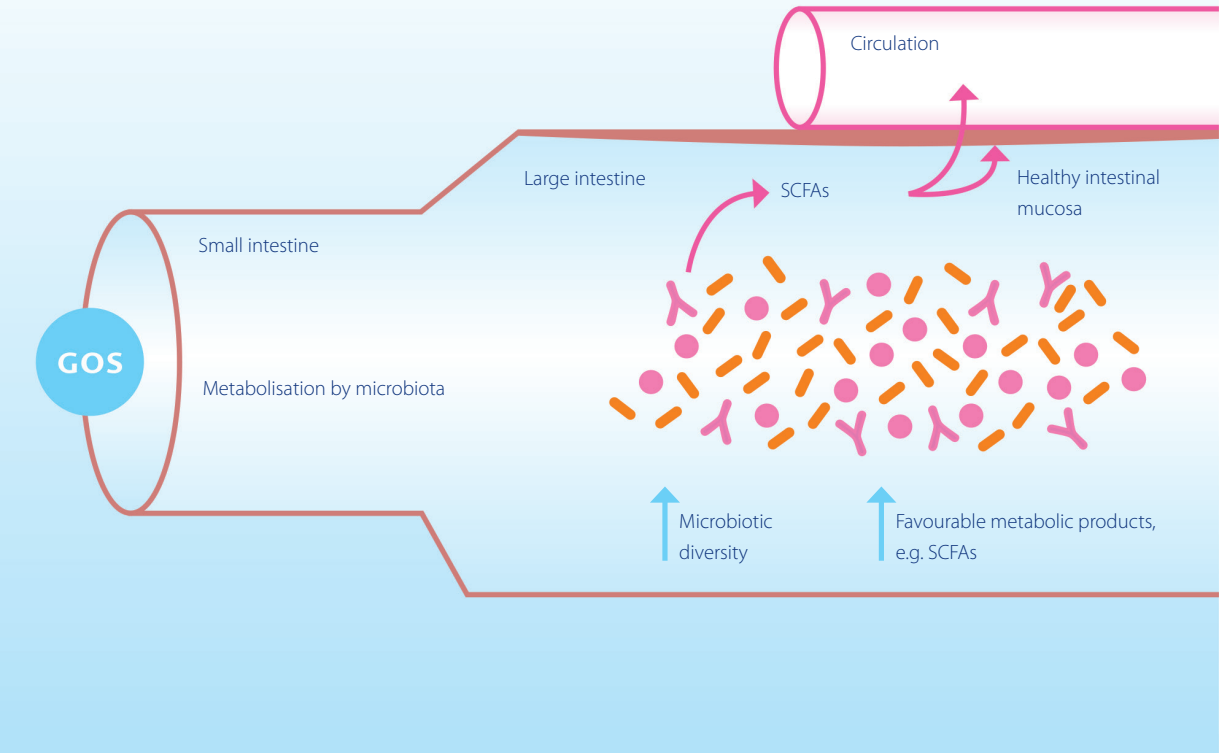

Fig. 3: *Modified based on Sonnenburg ED and Sonnenburg JL 2014*

If the mother is not at all or not exclusively breastfeeding, an perfectly formulated infant formula should be used. Due to the sub-optimal gut microbiota of infants born by C-section, the choice of formula is of particular importance for them. It should resemble the composition of breast milk as closely as possible and contain both special bacterial cultures such as lactobacilli as well as their respective "food sources" like galacto-oligosaccharides (GOS). These formulae have been proven to be safe and to have certain advantages. Studies have shown that infants receiving synbiotic infant formula are less likely to have infections than those receiving only prebiotic infant formula (Maldonado J et al. 2012; Gil-Campos M et al. 2012).

Conclusion:

The composition of microbiota at birth can be regarded as the important "control centre" when starting out in life. It sets the course for a person's health status in later life. The foundation of the microbial composition is laid at the start of life by the maternal preconditions, the gestational age, the type of delivery and accompanying (medicinal) interventions. The microbiota is also subject to constant change and is influenced by many other factors such as nutrition, stress and genetic constitution.

1. An infant's microbiota is significantly influenced by the type of delivery. In the case of a C-section, the lack of transferral of vaginal fluids to the infant is not the only influencing factor, as it is also influenced by accompanying medicinal interventions and the altered composition of the colostrum.

2. When compared to vaginal delivery, infants born by C-section have an altered microbiota and a delayed bacterial colonisation. One consequence under discussion in this context is the increased occurrence of various diseases. This is particularly the case for allergies, metabolic diseases such as diabetes and obesity, and increasingly also neurological disorders such as ADHD.

3. "Vaginal seeding" can have a positive effect on infants born by C-section. This refers to a new approach whereby infants are "inoculated" with maternal vaginal fluids immediately after birth. Making this a routine procedure is, however, still the subject of some controversy within the scientific and medical community, and is not yet generally recommended.

4. Breastfeeding is still considered to be the best option for infant nutrition. Besides the "common" nutrients, breast milk also contains pre- and probiotics, which are essential for the microbial colonisation of the small and large intestine.

5. In cases where breastfeeding is not possible, the use of infant formula containing pre- and probiotics is recommended. This way, the composition of breast milk can be imitated, with regard to substances which have been proven to be beneficial for healthy microbiota. This particularly applies to infants born by C-section, as they generally have a sub-optimal initial microbial colonisation.

6. Infants are what they "eat" – this is particularly true for the development of the microbiota, which is an essential foundation of a person's short-term and long-term health status, and therefore also regarded as the mirror of nutrition.

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