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Maternal Overweight, Inflammation and Neurological Consequences for the Preterm Child: Results of the ELGAN Study

Mütterliches Übergewicht, Inflammation und neurologische Konsequenzen für das frühgeborene Kind: Ergebnisse der ELGAN-Studie

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ABSTRACT

Maternal overweight and obesity are prenatal risk factors for obstetrical complications, preterm birth, neonatal morbidity as well as cognitive and behavioural developmental disorders in children. Paediatric morbidity and mortality as well as child development disorders are significantly associated with maternal obesity. Particularly in the neurodevelopmental and psychiatric area, it is becoming increasingly clear that, in children of mothers with an increased body mass index (BMI), there is a high correlation with childhood cognitive disabilities, attention disorders, and diseases on the autistic spectrum. The ELGAN (Extremely Low Gestational Age Newborn) study is a multicentre study which has been supported since 2000 by the National Institutes of Health (NIH) and whose objective is to research predictors for neonatal brain damage and neurological-cognitive sequelae in premature infants. The areas of focus are the connection between maternal overweight and obesity and pregnancy complications, APGAR scores and systemic inflammatory markers. In this overview, our aim is to summarise the work in this area and discuss it critically on the basis of current literature. We will examine the hypothesis whether maternal overweight and obesity in terms of a chronic inflammatory state is associated with neonatal inflammation which in turn is associated with an unfavourable development prognosis.

ZUSAMMENFASSUNG

Mütterliches Übergewicht und Adipositas sind pränatale Risikofaktoren für geburtshilfliche Komplikationen, Frühgeburt, neonatale Morbidität sowie kognitive und verhaltensauffällige Entwicklungsstörungen bei Kindern. Die kindliche Morbidität und Mortalität sowie Störungen der Kindesentwicklung sind signifikant mit maternaler Adipositas assoziiert. Besonders im entwicklungsneurologischen und -psychiatrischen Bereich wird zunehmend klar, dass es bei Kindern von Müttern mit erhöhtem Body-Mass-Index eine hohe Korrelation zu kindlichen kognitiven Einschränkungen, Aufmerksamkeitsstörungen und Erkrankungen aus dem autistischen Spektrum gibt. Die ELGAN-(Extremely Low Gestational Age Newborn-)Studie ist eine seit 2000 von den National Institutes of Health (NIH) geförderte multizentrische Studie, deren Ziel es ist, Prädiktoren für neonatale Hirnschäden und neurologisch-kognitive Folgen bei Frühgeborenen zu erforschen. Schwerpunkte sind der Zusammenhang zwischen mütterlichem Übergewicht und Adipositas und Schwangerschaftskomplikationen, Apgar-Werten

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und systemischen Inflammationsmarkern. In dieser Übersichtsarbeit verfolgen wir das Ziel, die Arbeiten in diesem Bereich zusammenzufassen und auf Basis der aktuellen Literatur kritisch zu diskutieren. Geprüft wird die Hypothese, ob mütterliches Übergewicht und Adipositas im Sinne eines chronischen Inflammationsstatus mit einer neonatalen Inflammationssituation zusammenhängen, die wiederum mit einer ungünstigen Entwicklungsprognose assoziiert ist.

Introduction

Maternal overweight and obesity are prenatal risk factors for obstetrical complications [1], preterm birth [2], neonatal morbidity [3] as well as cognitive and behavioural developmental disorders in children [4]. Paediatric morbidity and mortality as well as child development disorders are significantly associated with maternal obesity [5 – 8]. Particularly in the neurodevelopmental and psychiatric area, it is becoming increasingly clear that, in children of mothers with an increased body mass index (BMI), there is a high correlation with childhood cognitive disabilities, attention disorders, and diseases on the autistic spectrum [6].

The connection and the underlying mechanisms between maternal obesity and the above-mentioned paediatric morbidity are currently undergoing intensive research. While a main hypothesis primarily investigates the influence of epigenetic factors [9] which is not intended to be the focus of this work, our working groups investigated inflammation-associated mechanisms [8]. Here the focus is on the perinatal-neuroepidemiological approach to this issue, in particular. By analysing large data sets with perinatal and paediatric development data, we examine the hypothesis whether maternal overweight and obesity in terms of a chronic inflammatory state is associated with neonatal inflammation which in turn is associated with an unfavourable development prognosis.

The ELGAN (**E**xtremely **L**ow **G**estational **A**ge **N**ewborn) study is a multicentre study which has been supported since 2000 by the National Institutes of Health (NIH) and whose objective is to research predictors for neonatal brain damage and neurological-cognitive sequelae in premature infants [10]. The areas of focus are the connection between maternal overweight and obesity and pregnancy complications, Apgar scores [11] and systemic inflammatory markers [12]. Moreover, a series of analyses directly concern the postulated association between maternal BMI and neonatal-paediatric consequences [13 – 16].

In this overview, our aim is to summarise the work in this area and discuss it critically on the basis of current literature.

Maternal Weight and Body Mass Index

Based on the German Obesity Association, obesity is defined as an increase in body fat beyond the normal range [17]. The body mass index is used internationally to calculate and classify weight classes. While a BMI between 18.5 and 24.9 kg/m^2 is considered to be normal, a BMI between 25 and 29.9 kg/m^2 is considered to be overweight and a BMI over 30 kg/m^2 is considered to be obese. Obesity, in turn, is divided into degrees of severity, from I to III (grade I: BMI 30–34.9 kg/m^2; grade II: 35–39.9 kg/m^2; grade III > 40 kg/m^2) [17].

According to studies by the World Health Organisation (WHO), in 2008, about 1.4 billion adults worldwide were overweight and at least 500 million adults were obese. The WHO anticipated 2.3 billion overweight persons in 2015. In the normal population, obesity has generally doubled in recent decades. In 2014, according to press release 203/2016 from Eurostat, 46.1 % of persons living in the EU aged 18 and over were of normal weight, while slightly more than half of adults (51.6 %) were classified as overweight (35.7 % overweight and 15.9 % obese). In Germany, 47 % of women are affected by overweight and obesity (BMI > 25 kg/m^2). Approximately 29 % of all women are overweight (BMI between 25 and 30 kg/m^2) and about 18 % are obese (BMI over 30 kg/m^2) [18]. The prevalence of the combination of overweight and obesity in men between the ages of 15 and 49 in China between 2010 and 2014 was approximately 22–23 % [19]. Data from China published in 2002 showed that about 14.7 % of the Chinese population was overweight and another 2.6 % were obese [20]. At the time analysed, this represented 184 million people.

The proportion of pregnant women with obesity has also significantly grown. A German study from 2007 comparing the prevalence of overweight and obesity in pregnant women between 1980 and 2005 revealed that the number of overweight and obese pregnant women had tripled, with a disproportionately large increase in severe obesity [21]. In the United Kingdom, nearly 20 % of all pregnant women suffer from obesity [22]. In the USA, over 50 % of all pregnant women are either overweight or obese [23]. The prevalence of overweight and obesity in pregnant women varies in the different countries from 1.8 to 25 %.

A normal pregnancy and obesity share common characteristics. Mechanisms which are involved in the pathogenesis of obesity also represent essential parts of the physiological processes of maternal adaptation to the pregnancy. During pregnancy, weight gain is normal and desirable. There is a positive correlation between maternal weight gain in pregnancy and the birth weight of the foetus. In a recommendation from the Institute of Medicine, pregnant women with a BMI > 30 kg/m^2 are recommended a maximum weight gain of 5 to 9 kg [24]. A further reduction in weight gain for obese pregnant women is the subject of controversial discussion since this is potentially correlated with an increased risk of intrauterine growth retardation [25].

With regard to nutrition and lifestyle before and during pregnancy, the recommended actions of the nationwide network “Gesund ins Leben” (Healthy into Life) can be used. These recommendations address body weight prior to conception, changes in weight during pregnancy, the energy and nutritional requirements, as well as diet [67, 68].

Maternal Weight and Systemic Inflammation

Obesity [26,27] as well as pregnancy [28] can lead to a chronic inflammation reaction. Cytokines are protein molecules with diverse functions. Some cytokines are referred to as growth factors since they initiate or regulate the proliferation and differentiation of target cells. Other cytokines play an important role in immunological reactions and inflammatory processes in which they serve, above all, as signalling molecules between the immune and the nervous system [29]. The C-reactive protein (CRP) is an acute phase protein which further drives inflammation, while leptin is an adipokine, which is associated not only with feelings of satiety and energy homeostasis but also with a pro-inflammation reaction [30].

The systemic response to a pregnancy, which includes the mediators IL-6, CRP and leptin, among others, was elevated in overweight women prior to conception [12,31,32]. In the 4th week of pregnancy, a higher level of CRP could be detected in overweight women as compared to normal-weight pregnant women [33].

A BMI > 30 kg/m^2 represents a significant risk factor for a preterm delivery. Elevated levels of inflammatory proteins which lead to cervical ripening as well as to myometrial contractions were assumed to be the cause. As a result of the increased production of adipokines (such as leptin, for example) by the fat tissue as well as increased secretion of proinflammatory cytokines, maternal obesity appears to trigger a chronic inflammatory reaction [25].

In 80 blood samples taken from pregnant women during the second trimester, an increase in MCP-1, a proinflammatory cytokine, produced by macrophages, monocytes and endothelial cells, as well as an increase in leptin and CRP could be demonstrated in the group of severely obese pregnant women [12]. The association patterns of the pro- and anti-inflammatory markers with the various pregnancy characteristics greatly vary [34].

While in the case of spontaneous preterm infants there was no connection between maternal BMI and increased inflammatory proteins in the children in the ELGAN study, this was able to be confirmed in the group of deliveries due to maternal or foetal problems [14]. This so-called effect modification can be explained very well by the fact that the spontaneous preterm delivery, in contrast to preterm deliveries due to maternal or foetal indications, is strongly associated with prenatal infection and inflammation. It can be assumed that in the group of spontaneous preterm deliveries, all women, thus also those with a normal BMI, have an "inflammatory phenotype", while this is not the case in the group of maternal and foetal indications. For this reason, there may be no perceptible contrast with regard to maternal inflammation due to an elevated BMI in the case of spontaneously delivered children with or without a neonatal inflammation reaction. The signal cannot, so to speak, be reliably perceived due to significant "background noise".

In the ELGAN study, classification of the phenotypes of the preterm delivery was performed according to clinical presentation [69]. Of more than 1000 extremely immature preterm infants who were born before the 28th week of pregnancy, the distribution of the clinical presentation was as follows: Premature labour 40%, premature rupture of membranes 23%, preeclampsia 18%, placental abruption 11%, cervical insufficiency 5% and foetal indication/growth restriction 3%. In a subsequent analysis of these data, a significant prevalence contrast between two phenotype clusters was seen with regard to the neurological outcome: (A) premature labour, rupture of membranes, cervical insufficiency and placental abruption (3–5%) and (B) preeclampsia or foetal indication (1–2%) [70].

The connection between preterm birth phenotype and outcome is mediated, among other things, by protracted systemic neonatal inflammation [71]. In comparison to preterm infants of the phenotype cluster B, preterm infants of cluster A have a significantly higher risk for elevated serum concentrations of cytokines and other inflammatory markers after birth [72]. In statistical cluster analyses of cytokines from placental lysates, it was able to be shown that placentas after preeclampsia (cluster B) have elevated values for VEGF (vascular endothelial growth factor) and TGF-beta (transforming growth factor beta) as well as low inflammatory markers, while about half of the placentas from cluster A demonstrated an increased inflammation response [73]. The postnatal systemic inflammation reaction correlates with placental infection and inflammation [74] as well as with an increased risk of neurocognitive developmental disorders at the age of 10 years [75].

Somatic Consequences for the Child

Growth

A mother's body weight has consequences for the growth pattern of her child. In the ABCD study, Oostvogels studied more than 3800 mother–child pairs and determined that during the first years of life, sons as well as daughters of overweight mothers gained weight and BMI more quickly. These effects are modified by age and gender: Differences between the observed groups become larger over time and are more pronounced in girls than in boys [7].

Structural deformities

Maternal overweight and obesity are associated not only with an increased risk of foetal macrosomia and neonatal mortality [5], but also with structural changes, such as neural tube closure defects, cardiac anomalies, or orofacial malformations [35]. In a systematic analysis of 18 studies, Stothard et al. [36] showed no fewer than ten such developmental anomalies (▶ **Table 1**). Only in the case of gastroschisis was the likelihood of occurrence reduced.

Overweight and obesity

It is possible that the development of obesity is influenced in the prenatal period and that the maternal weight gain during pregnancy could have an effect on the later obesity of the child [37]. Such a connection can be explained by the model of so-called "metabolic imprinting". This concerns a modification of the intrauterine environment which can have a direct effect on the BMI of the unborn child [38] and which could thus also represent a risk factor for obesity in adulthood [39,40]. The hypothesis behind this is that the foetal metabolism is changed due to the mother's

▶ **Table 1** Association between maternal overweight or obesity and structural changes of the fetus. Results of a systematic analysis of 18 studies based on Stothard et al. [36]. The probability of occurrence was only reduced in the case of gastroschisis..

Malformation	Odds ratio	95% confidence interval
Neural tube defects	1.87	1.62–2.15
Spina bifida	2.24	1.86–2.69
Cardiovascular anomalies	1.30	1.12–1.51
Septal defects	1.20	1.09–1.31
Cleft palate	1.23	1.03–1.47
Cleft lip and palate	1.20	1.03–1.40
Anorectal malformations	1.48	1.12–1.97
Hydrocephalus	1.68	1.19–2.36
Hip dysplasia	1.34	1.03–1.73
Gastroschisis	0.17	0.10–0.30

Source: [36]

malnutrition and hyperglycaemia and the development of obesity is promoted [40].

Neurological and Cognitive Development

Overweight and obesity prior to pregnancy are associated with antenatal and peripartum complications such as gestational diabetes, preeclampsia, pregnancy-induced hypertension and complications relating to delivery [41, 42]. Moreover, maternal obesity additionally appears to have negative effects on the newborn [43], such as cognitive deficits [44, 45], autistic developmental disorders [46, 47] or cerebral palsy (CP) [48 – 52].

Cerebral palsy

Two comprehensive meta-analyses [53, 54] investigated the relationship between maternal BMI and the risk of cerebral palsy. Both analyses have a significant connection between maternal overweight or obesity and the occurrence of cerebral palsy. Maternal overweight and maternal obesity grade II and grade III were associated with an increased risk of 29, 45 or even 125% [53]. In contrast to this, the data from the ELGAN study did not reveal any increased risk for CP in children born very prematurely to overweight or obese mothers in comparison to mothers with a normal weight [55]. As in the effect modification described above through spontaneous versus induced delivery, the lack of a connection in the case of extremely premature infants could be due to a greater “inflammatory background noise” as compared to infants born at term.

Neurocognitive development

In a small, monocentre study of 62 maternal/child pairs in whom delivery occurred before the end of the 31st week of pregnancy, maternal obesity was associated with a positive autism screening and low speech development score [56]. In the ELGAN study, the pre-pregnancy heights and weights of the mothers of 852 children born prematurely were collected and analysed in a multinomial logistic regression model. It showed that, compared to newborns of mothers with a normal BMI, newborns of obese but not of overweight mothers had a greater likelihood of reaching Bayley Scales indices more than three standard deviations below the reference range (mental scale: OR = 2.1; 95% CI: 1.3, 3.5; motor scale: OR = 1.7; 95% CI: 1.1, 2.7) [13]. This association was even greater in newborns who did not demonstrably have any intermittent or longer-lasting systemic inflammatory marker profiles. Maternal obesity accordingly appears to be associated with an increased risk of impaired development of the newborn.

At the age of 10 years, an increased risk for decreased scores in the verbal ability scale II, IQ measurements for processing speed and fine motor control (developmental neuropsychological assessment II) as well as for pronunciation and spelling (Wechsler individual achievement test-III) were seen in an analysis of 535 children from the ELGAN study [15]. Children of mothers who gained excessive weight during pregnancy had an increased risk of low scores in the area of linguistic expression. However, children of mothers without adequate weight gain also had an increased risk of low scores in the areas of linguistic expression and reading ability. Physiological weight gain during pregnancy thus appears to have a protective influence on the neurocognitive development of the child.

Inflammation as a Pathomechanism

A possible pathomechanism for the connections between maternal weight and neuropaediatric outcome listed is perinatal inflammation [8].

The scenario of infection during pregnancy, inflammation reaction in the mother and child, preterm birth and neonatal brain damage have already been postulated for more than 20 years [57, 58] and have also been extensively documented in the meantime [59, 60]. This results in the following syllogism:

1. Maternal overweight and obesity are associated with preterm delivery and maternal-foetal inflammation;
2. Maternal overweight and obesity are associated with perinatal brain damage and later developmental disorders;
3. Preterm birth and inflammation are associated with perinatal brain damage and later developmental disorders;
4. Maternal overweight and obesity could lead to developmental disorders in preterm infants via a systemic inflammation reaction.

Which potential role the systemic inflammation reaction plays in the connection between maternal overweight or obesity and the developmental disorders in preterm infants remains to be evaluated in more detail. Maternal overweight or obesity can, just like the pregnancy itself [28], contribute to a chronic inflammation reaction in the mother via cytokines such as CRP, IL-6, and/or leptin [26, 27]. This maternal systemic inflammation can lead to direct foetal inflammation with damage to the child’s brain [61]. Children whose mothers had high levels of the equally proinflammatory mediators TNF-a [62] or IL-8 [63] have an increased risk for developing schizophrenia. Maternal obesity appears to contribute to prolonged systemic inflammation in the newborn [14], which

in turn represents a significant developmental risk for the child born preterm.

Summary

In summary, it can be concluded that there are multiple valid indications for a connection between overweight or obesity in mothers and a broad spectrum of developmental disorders in their children. We primarily discussed the results of the ELGAN study in which exclusively preterm infants with a gestational age of < 28 weeks of pregnancy were recruited. These results may therefore not be able to be fully applied to children with a gestational age of > 28 weeks of pregnancy.

Moreover, there are plausible reasons for explaining these connections through systemic foetal and neonatal inflammation reactions which are a significant focus of the content of the ELGAN study. In this investigation, we accordingly focused on these pathomechanisms. There are of course multiple other possibilities, such as a folate deficiency in obesity during pregnancy as a potential risk factor in newborns [64].

Weight gain during pregnancy is normally desirable. Nonetheless, an intervention for risk reduction in the case of overweight and obesity in pregnancy should be discussed for the reasons discussed here [65]. The evidence with regard to possible efficacy, for example, in the form of dietary advice during pregnancy for the prevention of gestational diabetes, remains unclear. To date there are no neonatal data and development data [66]. Corresponding studies would therefore benefit in particular from cooperation between obstetricians and developmental paediatricians.

Conflict of Interest

The authors declare that they have no conflict of interest.

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