Paediatric Respiratory Reviews 16 (2015) 251–257

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Review

Maternal obesity and immune dysregulation in mother and infant: A review of the evidence

Giulia S. Rizzo [a], Sarbattama Sen [b,*]

[a] Tufts University School of Medicine, 145 Harrison Ave, Boston, MA 02111, USA
[b] Brigham and Women's Hospital, Department of Pediatric Newborn Medicine, 75 Francis St, Boston, MA 02115, USA

EDUCATIONAL AIMS

- To describe the impact of obesity on immune function in pregnant women
- To review the epidemiologic and animal evidence supporting the relationship between maternal obesity and offspring asthma and immune modification
- To discuss potential mechanisms by which maternal obesity may impair both maternal and fetal immune function
- To briefly summarize maternal interventions that have been trialed to improve immune function in mother and infants

ARTICLE INFO

Keywords:
Maternal obesity
Asthma
Immune dysregulation
Inflammation
Fetal programming

SUMMARY

Obesity is a worldwide public health epidemic. Increasing numbers of reproductive-age women enter pregnancy overweight or obese and there is now convincing data that this adverse *in utero* environment impacts both fetal and lifelong development. Epidemiologic evidence has shown a simultaneous increase in obesity and asthma rates in developed countries and maternal obesity is a risk factor for infant asthma and wheeze. Here we review the state of research linking maternal obesity and immunomodulation in both mother and infant, with specific attention to the relationship between maternal obesity and offspring asthma. We will also propose several different mechanisms by which maternal obesity may predispose offspring to this chronic condition and briefly summarize interventions that have been trialed to limit this association.

INTRODUCTION

The World Health Organization has described obesity as the most pressing public health epidemic of this generation [1]. In the US, the prevalence of obesity among adults is 35.7% [2], and two out of three women are overweight or obese just prior to pregnancy [3]. The WHO defines obesity by body mass index (BMI) measurements and classifications, where BMI is measured in kg/m^2 with a BMI≥30 classified as obese [1].

Obesity in pregnancy has an impact on both mother and child. It poses a significant risk for many obstetric, post-partum, and fetal/neonatal complications, including caesarean delivery, intrapartum infections, [4] post-partum wound infections, [4,5] and stillbirths [4]. Maternal obesity also predisposes offspring to several long-term consequences for the offspring, such as obesity, metabolic syndrome, and asthma [6]. The abnormal metabolic environment of obesity is characterized as a state of chronic or low-grade systemic inflammation [7], which leads to stimulation of the immune system with pro-inflammatory cytokines, particularly tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), and interleukin-6 (IL-6) [7]. Excess adipose tissue releases adipokines, such as the pro-inflammatory hormone leptin [8].

Asthma is a significant public health problem affecting children and adults worldwide. Asthma is the third leading cause of hospitalization for children under the age of 15 [9] and over 75% of children with asthma will continue to be symptomatic into adulthood [10]. This chronic medical condition is characterized by inflammation of the airway and episodic bronchoconstriction. The airways of asthmatics are infiltrated by inflammatory cells specifically T lymphocytes, mast cells, eosinophils, macrophages, and neutrophils [9]. Long-term effects in the airways can include increased mucus production, subepithelial layer thickening, and

* Corresponding author. Tel.: +617-525-4123.
E-mail addresses: Giulia.s.rizzo@gmail.com (G.S. Rizzo), Ssen2@partners.org (S. Sen).

http://dx.doi.org/10.1016/j.prrv.2014.10.005
1526-0542/

smooth muscle hypertrophy and hyperplasia. Clinical symptoms such as wheezing, coughing, and difficulty breathing are caused by bronchoconstriction and airway hyper-responsiveness to lower airway inflammation [9].

Pregnancy itself is characterized by immunomodulatory changes occurring in three distinct but fluid immunologic stages. Initially, the implantation of the blastocyst is linked to increased inflammation. Subsequently, and for the majority of pregnancy, there is relative immunosuppression to prevent rejection of paternal antigens and allow for the fetal growth and development. Finally, in the peri-partum period, there is an increase in inflammation [11]. Overall, during a normal pregnancy, the mother has an active but modulated immune system at the maternal-fetal interface that involves complex interplay and communication among natural killer (NK) cells, macrophages, and regulatory T cells [11].

Recent research has suggested that the upward trend of maternal obesity and pediatric asthma are not simply coincidental. This review will address the association between maternal obesity, immune dysregulation of the mother and infant, and offspring asthma/wheeze. We will review the epidemiologic data suggesting the correlation between maternal obesity and offspring asthma and then discuss the mechanistic findings that could underlie this association.

THE EFFECTS OF MATERNAL OBESITY ON THE MATERNAL IMMUNE SYSTEM

As shown in Table 1, obesity has been shown to alter many aspects of maternal immune function [12–14]. Women who enter pregnancy obese are more likely to develop wound infections [15–17], endometritis, chorioamnionitis [18], sepsis

Table 1
Maternal obesity and its effects on maternal immune function.

Author	Country	Year	Population	Major Findings
Acosta *et al* [30]	UK	1986-2009	-103 women with maternal sepsis -412 control women	Obese women were twice as likely to develop uncomplicated sepsis compared to women of normal BMI (OR = 2.12, 95% CI: 1.14-3.89).
Robinson *et al* [26]	Canada	1988-2002	-142,404 singleton pregnancies	-Moderately obese pregnant women had an increased risk of wound infection (adjusted OR: 1.67, 95% CI: 1.38-2.00). -Severely obese pregnant women were almost 5 times more likely to have a wound infection (adjusted OR: 4.79, 95% CI: 3.30-6.95).
Sebire *et al* [6]	UK	1989-1997	-287,213 singleton pregnancies -61.6% BMI 20-24.9	Obese pregnant women had an increased risk of: -Chest infection (OR = 1.34, 95% CI: 0.99-1.92) -Genital tract infection (OR = 1.30, 95% CI: 1.07-1.56) -Wound infection (OR = 2.24, 95% CI: 1.91-2.64) -Urinary tract infection (OR = 1.39, 95% CI: 1.18-1.63)
Vermillion *et al* [28]	USA	1996-1997	-140 women who underwent cesarean sections	Pregnant women with high subcutaneous tissue thickness were at an increased risk for wound infection (RR = 2.8, 95% CI: 1.3-5.9).
Stapleton *et al* [32]	USA	1997-2002	-Women birthing live singleton infants -40,459 cases of GBS colonization -84,268 controls	Maternal obesity is independently associated with increased maternal Group B Streptococcal colonization in the genitourinary tract: -BMI = 30-39.9: OR = 1.20, 95% CI: 1.13-1.28 -BMI≥40: OR = 1.45, 95% CI: 1.28-1.63)
McLean *et al* [22]	USA	1998-2005	-238 women with BMI≥30 who delivered via cesarean	Maternal BMI was associated non-linearly with wound complications ($p < 0.01$).
Basu, Jayati *et al* [23]	South Africa	2006	-767 women with singleton fetuses (44% obese/morbidly obese)	Morbidly obese pregnant women were more likely to have urinary tract infections (P = 0.002).
Salim *et al* [27]	Israel	2006-2007 2009-2010	-1616 women who underwent cesarean section	For every 5kg/m[2] increase in the BMI of pregnant women, there was a 27% increase in the risk of infection (OR: 1.27; 95% CI: 1.05-1.54).
Magann *et al* [29]	USA	2007-2008	-4,490 women with singleton births	-Obese pregnant women were at an increased risk for wound infection (BMI≥30: P = 0.001), urinary tract infections (BMI≥35: $P < 0.001$), and endometritis (BMI≥40: $P < 0.001$).
Paiva *et al* [31]	Brazil	2009-2010	-374 pregnant women -High-risk, live birth, singleton pregnancies	Maternal obesity during late pregnancy is an independent risk factor for postpartum infectious complications: -Surgical wound infection (p = 0.042) -Urinary infection (p = 0.004) -Antibiotic therapy ($p < 0.001$) -Abdominal wall infection (OR: 2.24; 95% CI: 1.91-2.64) -Composite morbidity (p = 0.016)
Sen *et al* [34]	USA	2011	-15 obese women -15 lean women	Obese mothers had impaired cytokine production, impaired lymphocyte proliferation, a lower proportion of CD8+ and NKT cells, and a higher proportion of B cells when compared to lean mothers ($P < 0.05$).
Meenakshi *et al* [5]	India	2012	-87 overweight BMI>25 -83 obese BMI>30 -45 normal	Overweight and obese pregnant women were at an increased risk for impaired wound healing ($p < 0.05$) and pyrexia ($p < 0.01$).
Mochhoury *et al* [24]	Morocco	2013	-1408 non diabetic women w/o several HTAs -Singleton births (37-42 wks gestation)	Overweight/obese pregnant women and women who gain >16 kg during pregnancy had a higher risk for infections ($P < 0.01$).
Conner *et al* [25]	USA	2013	-2,444 women: 266 developed wound complication: 728 non-obese, 1,716 obese (BMI ≥ 30) -Retrospective cohort study 2004-2008	Increasing maternal BMI is associated with an increased risk of wound complications: -BMI = 30.0-39.9: OR = 1.4, 95% CI: 0.99-2.0 -BMI = 40.0-49.9: OR = 2.6, 95% CI: 1.7-3.8 -BMI≥50: OR = 3.0, 95% CI: 1.9-4.9

BMI = Body Mass Index; OR = Odds Ratio; CI = Confidence Interval; p = p-value; RR = Relative Risk.