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Is there a connection between gestational diabetes mellitus, human immunodeficiency virus infection, and tuberculosis?

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SUMMARY

Pregnancy is associated with insulin resistance similar to that found in type 2 diabetes mellitus (DM). The prevalence of gestational diabetes mellitus (GDM) in key tuberculosis (TB) endemic countries, such as India and China, has been increasing rapidly in the last decade and may be higher in human immunodeficiency virus (HIV) infected women. Pregnancy is also an independent risk factor for developing active TB; however, little is known about the interaction of GDM, HIV and TB. We review the epidemiology, immunology, and significant research gaps in understanding the interactions between GDM, pregnancy, and TB in women living with and those without HIV.

RÉSUMÉ

La grossesse est associée à une résistance à l'insuline similaire à celle du diabète (DM) de type 2. La prévalence du diabète gestationnel (GDM) dans des pays clés d'endémie de tuberculose (TB), comme l'Inde et la Chine, a rapidement augmenté au cours de la dernière décennie et est peut-être plus élevée chez les femmes infectées par le virus de l'immunodéficience humaine (VIH). La grossesse est également un facteur de risque indépendant de développement d'une TB active mais on connaît mal l'interaction du GDM, du VIH et de la TB. Dans cet article, nous revoyons l'épidémiologie, l'immunologie et les lacunes significatives de la recherche en matière de compréhension des interactions entre GDM, grossesse et TB parmi les femmes vivant avec et sans le VIH.

RESUMEN

El embarazo se asocia con una resistencia a la insulina semejante a la que se observa en los casos de diabetes (DM) de tipo 2. La prevalencia de DM gestacional (GDM) en grandes países con tuberculosis (TB) endémica como la India y la China ha aumentado muy rápido en los últimos 10 años y es tal vez mayor en las mujeres infectadas por el virus de la inmunodeficiencia humana (VIH). El embarazo constituye también un factor de riesgo independiente de padecer TB activa, pero se conoce poco sobre la interacción de la GDM, la infección por el VIH y la TB. En el

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presente artículo se analizaron aspectos epidemiológicos, inmunológicos y las importantes lagunas científicas en la comprensión de las interacciones entre la GDM, el embarazo y la TB en mujeres con infección por el VIH o sin esta infección.

Keywords

pregnancy; immunology; TB; DM

EVERY YEAR, OVER 200 000 pregnant and postpartum women are estimated to develop active tuberculosis (TB) worldwide.¹ A woman is most likely to develop active TB during pregnancy and the immediate postpartum period than any other time in her life.² Pregnant women, particularly those with human immunodeficiency virus (HIV) infection, are also at risk of developing dysglycemia or gestational diabetes mellitus (GDM). In non-pregnant populations, diabetes mellitus (DM) is a known risk factor for progression from latent tuberculous infection (LTBI) to active TB, as is HIV.³ Historic case reports suggest that there is an association between GDM and TB as well.⁴ However, we do not know if GDM increases the risk of acquiring new tuberculous infection or expediting the progression of LTBI to active TB. Our lack of understanding about the impact of GDM on TB is a problem in TB-endemic countries, where TB, HIV and DM epidemics are now converging.

In the present review, we discuss the epidemiology, clinical outcomes, immunology, and the significant research gaps in understanding the interactions between GDM, pregnancy, and TB in women living with and without HIV.

PREGNANCY AND TUBERCULOSIS

Epidemiology

In 2017, 3.5 million women were diagnosed with active TB, the majority between the ages of 15 and 45 years.⁵ Although there is no systematic collection of data on TB in pregnancy at national or international levels,⁶ a 2011 model estimated the global incidence of TB in pregnancy to be 2.1 cases per 1000 pregnant women compared with a total global incidence of 1.2 cases per 1000 people. TB incidence was highest in pregnant women in sub-Saharan Africa (3.6/1000) and South-East Asia (2.4/1000).¹ This model may underestimate the true burden of TB in pregnancy because it cannot account for missed diagnoses.⁷

Pregnant women tend to have paucibacillary disease, and the World Health Organization (WHO) TB symptom screen is less sensitive in this population,^{7–9} which complicates active case finding. Based on published cases, the risk of TB in HIV-infected pregnant women appears to be higher, with 1–11% developing active TB during pregnancy or the early postpartum period.^{6,10}

Clinical outcomes

Diagnostic challenges during pregnancy result in longer delays to treatment initiation, leading to poor outcomes for the mother and infant. A pregnant woman with active TB has a higher risk of complications, including a two-fold increase in preeclampsia, eclampsia or

vaginal bleeding, and a 10-fold increased risk of miscarriage.^{6,11–13} The risk of death is 25 times higher in non-HIV-infected pregnant women with TB than those without TB; in the precombined antiretroviral therapy (cART) era, it was 37 times higher for HIV-infected pregnant women with TB than for those without.¹⁴

For the infant, there is a two-fold increased risk of low birth weight, prematurity and being small for gestational age.^{11,12,15} There is also a 3.4-fold increased risk of death¹⁶ and congenital TB, many in infants of women who developed active TB after in vitro fertilization.^{17–20}

PREGNANCY AND GESTATIONAL DIABETES MELLITUS

Epidemiology

The WHO defines GDM as carbohydrate intolerance with onset or recognition during pregnancy, including women who develop type 1 or type 2 DM during pregnancy.²¹ The International Diabetes Foundation estimates that one in seven pregnancies worldwide is complicated by GDM.^{22,23} In recent years, prevalence estimates of GDM have been increasing, largely due to advanced maternal age, maternal obesity and inactivity.²⁴

However, the true prevalence and distribution of GDM is not known, in part due to a lack of international consensus on screening or diagnosis, leading to reluctance in performing oral glucose tolerance tests (OGTTs).^{23,25} This is of particular concern in low- and middle-income countries, where the DM and TB burdens are high.²⁶ A recent systematic review from India, for example, reported a GDM prevalence of 0–42%, depending on the region of India and screening test used. Studies comparing the WHO 1999 and International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria found a difference in prevalence ranging from 0.16% to 25.9%.²⁷

Clinical outcomes

Operationally, it is important to identify women with GDM due to the impact that uncontrolled hyperglycemia has on maternal and infant outcomes. Treatment of GDM can significantly reduce or eliminate many of these consequences.²⁸ Preeclampsia occurs in 26–40% of women with GDM.²⁹ The risk of hypertensive disorders can be as much as three times higher in women with GDM vs. those without.^{30,31} Women with GDM are also more likely to have a caesarean delivery (52–60%).^{31,32} Other adverse maternal outcomes include premature rupture of membranes and preterm delivery.²⁹

Long-term effects of GDM are seen in subsequent pregnancies, as well as later in a woman's life. Women with GDM have a 10-fold increased risk of developing GDM in subsequent pregnancies.³³ Evidence indicates that they also have an increased risk of developing maternal obesity, metabolic syndrome and type 2 DM as well.^{34–36} In fact, approximately 35–60% of women with GDM develop type 2 DM within 10 years after delivery.^{37,38}

Uncontrolled maternal hyperglycemia also leads to increased fetal insulin secretion, which acts as a growth hormone for the fetus. The associated overgrowth of insulin-sensitive tissue, such as adipose tissue around the chest, shoulders and abdomen, increases the risk of

shoulder dystocia, perinatal death and birth trauma.^{29,36,39} Increased risk of perinatal mortality, congenital malformation, birth injuries, hyperbilirubinemia, respiratory distress, and Apgar scores of <7 have also been reported.^{36,40}

Fat mass is greater in neonates of women with GDM, and could forecast the development of cardiovascular diseases later in life.⁴¹ These children are also at higher risk of being overweight throughout their childhood and adolescence.⁴² More recent data suggest that pre-gestational DM or GDM can adversely affect the attention span and motor functions of offspring at school age. These effects were negatively correlated with the degree of maternal glycemic control, and were more pronounced in younger children.⁴³ Some have even hypothesized that the increased incidence of childhood type 2 DM can be attributed to the increased exposure to maternal hyperglycemia in the intrauterine environment.⁴⁴

DIABETES MELLITUS AND TUBERCULOSIS

Epidemiology

Recent analyses suggest that type 2 DM triples the risk of TB,⁴⁵ with 10.2% of adult TB cases in the WHO's 22 high TB burden countries attributable to DM.⁴⁶ By 2025, India, China, Indonesia, Pakistan and Brazil alone are projected to represent almost half of the world's DM burden.⁴⁷ In these countries with high burdens of TB and DM, DM looms as a larger threat to TB control than HIV infection. In India, for example, the population attributable proportion in the total population is greater for DM (9.1%) than HIV (5.0%).⁴⁶

Clinical outcomes

Some studies have reported poorer outcomes for people with TB and DM, including more cavitory disease^{48,49} and longer time to culture conversion, resulting in an increased risk of drug-resistant TB.^{48–50} One study in Tanzania found a decreased rate of improvement in hemoglobin in patients with TB and DM vs. those with TB alone,⁵¹ which is particularly relevant for women of reproductive age. Studies have also shown an increased relative risk of death among TB patients with DM compared with those without, ranging from 1.89 (95% confidence interval [CI] 1.36–2.1) to 4.95 (95% CI 2.6–9.1) when adjusted for age.⁵² One study in the United States found that, after adjustment for several confounding factors, the odds of death from TB were 6.5 times greater in patients with DM than those without DM (adjusted odds ratio, 95% CI 1.1–38.0).⁵³

Impact of human immunodeficiency virus on diabetes mellitus

The most commonly cited reason for the increased risk of insulin resistance in HIV-infected people is the side effects of ART, with protease inhibitors (PIs) being the biggest offenders.⁵⁴ Reverse transcriptase inhibitors (e.g., zidovudine, lamivudine, and efavirenz), however, have also been implicated.^{55,56} It has been postulated that PIs confer the acute metabolic risks, while nucleoside reverse transcriptase inhibitors confer the cumulative risks, of DM in predisposed, exposed persons.⁵⁶

A cross-sectional study in Tanzania found that HIV-infected adults on ART had a significantly higher prevalence of glucose metabolism disorders and frank DM than HIV-

negative adults, which remained highly significant even after adjusting for age, sex, adiposity and socio-economic status.⁵⁷ Recent data suggest that HIV-infected people may have a greater degree of insulin resistance than non-HIV-infected people, regardless of ART.^{58,59}

Data on GDM in HIV-infected pregnant women are scant and often contradictory. Several small studies have reported a higher prevalence of GDM in HIV-infected women than non-HIV-infected women.^{60,61} A study of 609 women in Spain reported a GDM prevalence of 7% in HIV-infected women vs. 2–5% in non-HIV-infected women.⁶² Another study from the AIDS Clinical Trial Group also showed a significant increase in GDM in women who received PI-containing therapy, particularly with long-term antiretroviral use.⁶³ However, a retrospective study of 263 HIV-infected pregnant women in Ireland who had undergone OGTT did not confirm this observation.⁶⁴ A recent systematic review concluded that there are insufficient data to confirm whether there is a true association between HIV and GDM, and recommended well-designed long-term cohort studies of HIV-infected and non-HIV-infected pregnant women.⁵⁴

HOW GESTATIONAL DIABETES MELLITUS, HUMAN IMMUNODEFICIENCY VIRUS, TUBERCULOSIS AND PREGNANCY MAY INTERACT: IMMUNOLOGIC CONSIDERATIONS

A healthy pregnancy is associated with insulin resistance similar to that found in type 2 DM. These changes occur to facilitate transport of glucose across the placenta to enable normal fetal growth and development. Transfer of glucose across the placenta stimulates fetal pancreatic insulin secretion, which acts as an essential growth hormone.

As mentioned above, GDM is an operational classification rather than a pathophysiological condition. It is diagnosed if there is maternal hyperglycemia due to pronounced insulin resistance.²⁴ Pregnancy may act as a 'stress test' to reveal a woman's predisposition to type 2 DM. Most insulin resistance returns to normal following birth, although 20% of women will continue to have dysglycemia in the immediate postpartum period.^{38,65}

Diabetes mellitus and active tuberculosis

The impact of DM on TB immunity in pregnant or non-pregnant women is not clearly understood. Monocytes from non-pregnant women with DM exhibit reduced binding and phagocytosis of *Mycobacterium tuberculosis*, resulting in decreased uptake of the bacteria and delayed antigen presentation to lymphocytes.⁶⁶ This observation has been supported by three small retrospective studies which found that baseline mycobacterial burden was higher in patients with DM and TB than controls without DM.^{67–69} In animal studies, alveolar macrophages from diabetic mice also exhibited reduced phagocytosis of *M. tuberculosis*. When transferred to non-diabetic mice, the macrophage defect persisted and hindered T-cell priming,⁷⁰ suggesting that DM is associated with an intrinsic defect in macrophage function. It is not known if transient affliction with GDM causes similar intrinsic defects in macrophage function for pregnant women.

Despite the initial delay in response, animal studies have shown that, ultimately, people with DM demonstrate a hyper-reactive inflammatory immune response after 2 months of disease.⁷¹ It is unclear if this is related to the higher bacterial burden patients with DM accrue before mounting an inflammatory response, or if dysglycemia alone causes a dysregulated immune response.⁷² Nonetheless, the exaggerated T-cell response is quantitatively higher—as demonstrated by higher levels of interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α)—but not necessarily functionally more effective than the response in people without DM.⁷²

Diabetes mellitus, human immunodeficiency virus and active tuberculosis

Early reports suggested a reduced risk of DM among HIV-TB co-infected populations. HIV-infected people with DM tended to have higher CD4 counts and faster immune recovery post-cART initiation.^{73,74} More recent data, however, suggest an increased risk of DM in HIV-infected people, including those who are virally suppressed.^{75,76} Proposed etiologies include chronic inflammation associated with HIV, changes in mitochondrial function, or the effects of CD4 and CD8 cells on glycolysis.^{55,56,58} Among HIV-infected non-pregnant adults in South Africa, DM was found to double the odds of having TB compared with having HIV alone. A systematic review from Africa, however, concluded that there are insufficient data on the association of DM and TB in HIV-infected people.⁷⁷

Gestational diabetes mellitus and active tuberculosis

During pregnancy, immune changes occur to allow a woman to ‘tolerate’ the semi-allogeneic fetus while maintaining vigilance against true infections. Innate immune cells, including monocytes, are likely maintained during pregnancy.⁷⁸ However, levels of monocyte chemoattractant protein 1 (MCP-1) are reduced.⁷⁸ A pregnant woman with GDM may therefore be at risk of developing particularly severe TB as the pregnancy-related changes impair her ability to attract monocytes to the lung and the hyperglycemic state impairs phagocytosis.

Diabetes mellitus and latent tuberculous infection

Unlike the hyper-inflammatory response seen in response to new tuberculous infection, persons with DM and LTBI seem to have a decreased inflammatory response. One study found that people with DM and LTBI have decreased levels of circulating IFN- γ , interleukin (IL) 2, TNF- α and IL-17F,⁷⁹ cytokines that are essential for maintaining TB immunity. Stimulation with TB-specific antigens also results in impaired CD4+ T-cell responses, including diminished mono- and dual-functional CD4+ T-helper (Th) 1, Th2 and Th17 cells in people with DM and LTBI compared with those with LTBI alone.⁸⁰ This seems to be driven in part by IL-10 and transforming growth factor- β , as neutralization of those cytokines resulted in increased frequencies of Th1 and Th2 cells.

Gestational diabetes mellitus and latent tuberculous infection

Studies on the impact of GDM on LTBI are lacking. Similar to DM, it is likely that women with GDM also experience a decreased inflammatory response to *M. tuberculosis*. This may be of particular concern during pregnancy because hormonal changes also create an anti-

inflammatory environment (Figure). Estriol, a hormone present only during pregnancy, reduces the number of CD4+ and CD8+ T-cells.⁸² Estradiol, another estrogen that increases in concentration during pregnancy, is associated with a 2–3-fold increase in the number of regulatory T-cells (T_{reg}).⁸³ T_{reg} cells dampen the pro-inflammatory immune response, often by producing IL-10. Progesterone also induces the placenta to produce IL-10,⁸⁴ which suppresses cell-mediated Th1 cytokines (IFN- γ , IL-2, TNF- α).⁸⁵

Data from cohorts of pregnant women from India and Kenya suggest *M. tuberculosis*-specific decreases in IFN- γ and IL-2 responses. In a study of 356 non-HIV-infected Indian women with LTBI, the median IFN- γ concentration was significantly lower in the third trimester and at delivery than 3 months postpartum ($P = 0.001$).⁸⁶ The same pattern was observed in HIV-infected pregnant women with LTBI in India and Kenya.^{87,88} Those who went on to develop active TB had greater reductions in IFN- γ and IL-2 during pregnancy than women without active TB.⁸⁷ GDM was not tested for in the Indian or Kenyan studies.

RESEARCH GAPS

Given that pregnancy, DM and HIV all cause immune changes that increase the risk of developing active TB (Table), it is possible that HIV-infected pregnant women with GDM are at particularly high risk of progressing to active TB. However, data on TB in GDM in both HIV-infected and non-HIV-infected populations are lacking. Research priorities should include:

- Systematic prevalence data of GDM in TB-endemic countries, particularly among HIV-infected women
- Assessment of integrated screening for HIV, TB and DM in pregnancy
- Outcomes-based research to establish consensus on an appropriate algorithm for GDM screening worldwide
- Cohort and translational studies of HIV-infected women to determine if there is an association between various cART regimens and GDM, with a focus on perinatally infected women with a longer duration of cART exposure
- Immunologic data to delineate the impact of GDM on TB immunity and clinical outcomes, including in HIV-infected and non-HIV-infected pregnant women and their infants
- Impact of GDM treatment on risk of active TB in pregnant and postpartum women
- Impact of pre-DM on the immune response to TB and infant outcomes

Filling these critical gaps will allow us to optimize screening and treatment options for pregnant women with GDM, and particularly those with HIV in TB-endemic countries.

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Figure. During pregnancy, increased levels of sex steroids reduce the inflammatory response⁸¹ (adapted with the kind permission of Elsevier Inc.). This image can be viewed online in color at <http://www.ingentaconnect.com/content/ijatld/ijtld/2019/00000023/00000001/art000...>

Table
Effect of TB, DM and pregnancy on key cell populations and TB pathogenesis ⁸⁹

Cell type	Function	Effect of TB	Effect of DM	Effect of pregnancy	Effect of HIV
Th1	Cell-mediated immune response • Macrophage activation	↑Th1 ↑IFN-γ ↑TNF-α ↑IL-2	↑Th1 ↑IFN-γ ↑TNF-α ↑IL-2	↓Th1 ↓IFN-γ ↓TNF-α ↓IL-2	↓Th1 ↓IFN-γ ↓TNF-α ↓IL-2
Th2	Humoral immune response • Stimulate M2 • B cell response	↑↓Th2 ↑↓IL-4 ↓IL-5	↓Th2 ↓IL-4	↑Th2 ↑IL-4 ↑IL-6	↑Th2 ↑IL-6
T _{reg}	Suppress and regulate immune response • Prevent pro-inflammatory cytokine secretion	↑Treg ↑TGF-β ↑IL-10	↓Treg ↓IL-10	↑Treg ↑TGF-β, ↑IL-10	↑Treg ↑TGF-β, ↑IL-10
Pathogenesis of TB infection and disease		NA	Chronic hyperglycemia → altered immune response to <i>M. tuberculosis</i> , delayed innate immune response	Th1/Th2 imbalance, reduced IFN-γ, TNF-α, IL-2 response to stimulation with TB antigen	CD4 depletion, tipped Th1/Th2 balance, HIV impairs TNF-α facilitates bacterial survival ⁸⁹

TB=tuberculosis; DM=diabetes mellitus; HIV=human immunodeficiency virus; TH=T-helper; IFN-γ=interferon-gamma; TNF-α=tumor necrosis factor-alpha; IL=interleukin; T_{reg} = regulatory T-cells; TGF-β = transforming growth factor-beta; NA = not available.