Thieme

Tuberculosis in Pregnancy – a Summary

Tuberkulose in der Schwangerschaft – eine Übersicht

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ABSTRACT

In recent years, the incidence of tuberculosis in pregnancy in the industrialised countries has increased. Tuberculosis in pregnancy is associated with an increased risk for the mother and child. Even if no figures are available for Germany, an increase in the number of tuberculosis cases among pregnant women can be assumed due to the migratory flows; current data from the USA, for example, also show an increasing incidence of tuberculosis in pregnant women in recent years. The physiological and immunological changes that occur during pregnancy are likely to have a negative impact on the course of the disease and may make it more difficult to confirm the diagnosis. There are no internationally standardised recommendations for diagnosing latent tuberculosis infections. When screening for TB is performed in specific risk populations, an Interferon-γ Release Assay (IGRA) should preferably be carried out according to the current study data. If corresponding symptoms are present and an IGRA test is positive, further diagnostics are indicated, also in pregnancy. If tuberculosis is confirmed, the fact that a woman is pregnant must not delay the initiation of anti-tuberculosis therapy, as an early start of therapy is associated with a more favourable outcome for both mother and child. The common first-line therapeutic drugs may also be used during pregnancy and are considered safe. The treatment of latent tuberculosis during pregnancy is disputed.

ZUSAMMENFASSUNG

In den letzten Jahren hat die Inzidenz der Tuberkulose in der Schwangerschaft in den Industrienationen zugenommen. Eine Tuberkulose in der Schwangerschaft ist mit einem erhöhten Risiko für Mutter und Kind verbunden. Auch wenn für Deutschland keine Zahlen existieren, ist aufgrund der Migrationsbewegungen von einer Zunahme von Tuberkulose-erkrankungen unter Schwangeren auszugehen, so zeigen auch aktuelle Daten aus den USA eine steigende Tuberkulose-inzidenz bei Schwangeren in den letzten Jahren. Die durch eine Schwangerschaft bedingten physiologischen und immunologischen Veränderungen haben dabei wahrscheinlich einen negativen Einfluss auf den Krankheitsverlauf und können die Diagnosestellung erschweren. Zur Diagnostik der latenten tuberkulösen Infektion gibt es international keine einheitlichen Empfehlungen. Wenn ein Screening in spezifischen Risi-

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kopopulationen erfolgt, sollte nach der gegenwärtigen Studienlage hierbei prioritär ein Interferon-γ Release Assay (IGRA) zum Einsatz kommen. Sowohl bei entsprechender Symptomatik als auch bei einem positiven IGRA-Test ist auch in der Schwangerschaft eine weiterführende Diagnostik indiziert. Im Falle einer Tuberkulose darf die Tatsache des Vorliegens einer Schwangerschaft die Einleitung einer antituberkulösen Therapie nicht verzögern, da deren frühzeitiger Beginn mit einem günstigeren Outcome für Mutter und Kind assoziiert ist. Die gängigen Erstlinientherapeutika können auch in der Schwangerschaft zur Anwendung kommen und werden als sicher angesehen. Die Therapie einer latenten tuberkulösen Infektion in der Schwangerschaft ist umstritten.

Introduction and Epidemiology

In 2016 the World Health Organization (WHO) reported 6.3 million new cases of tuberculosis worldwide – an increase of more than 200 000 cases compared to 2015 [1]. The most up-to-date figures for Germany are also from 2016; based on information of the Robert Koch Institute (RKI) 5915 new cases were registered [2]. In Germany, the disease incidence is particularly high among foreign nationals, namely 42.6/100 000 inhabitants, and is thus 19 times higher than in the German population. Compared to 2015, this difference has increased by more than 16 times [2]. Among foreign nationals, the disease affects in particular young adults, with a median age of 28 years (58 years in patients of German origin) [2].

The global prevalence of active tuberculosis in pregnant women is only estimated; the WHO also does not report concrete figures for this. According to a study conducted in 2014, around 216 500 pregnant women worldwide suffered from tuberculosis in 2011, nearly half of them were of African origin [3]. In the US, the incidence of tuberculosis in pregnant women increased continuously between 2003 and 2011 and is altogether reported as 26.6/100 000 births [4]. Analogous to the general population, tuberculosis infections in high-prevalence regions such as South Africa are markedly more common in HIV-infected than in HIV-negative pregnant women [5]. There are no figures on the incidence or prevalence of TB in pregnant women in Germany.

Owing to the migratory flows in recent years and the increase in the number of young patients with tuberculosis, it is expected that tuberculosis in pregnancy will also be of increasing relevance in the future in Germany.

This review article focuses on the special changes that occur in the immune system during pregnancy and also on the diagnosis and treatment of pregnant tuberculosis patients. The explanations and recommendations are given on the basis of the current literature, the national and international guidelines and the clinical experience of the authors against the backdrop of the increasing relevance of the disease.

Review

Changes in the immune system during pregnancy

During pregnancy, the maternal immune system undergoes a range of profound changes that are of crucial importance for maintaining the maternal-foetal immune tolerance. These changes are triggered primarily by hormones such as oestrogens and progesterone [6, 7]. Eve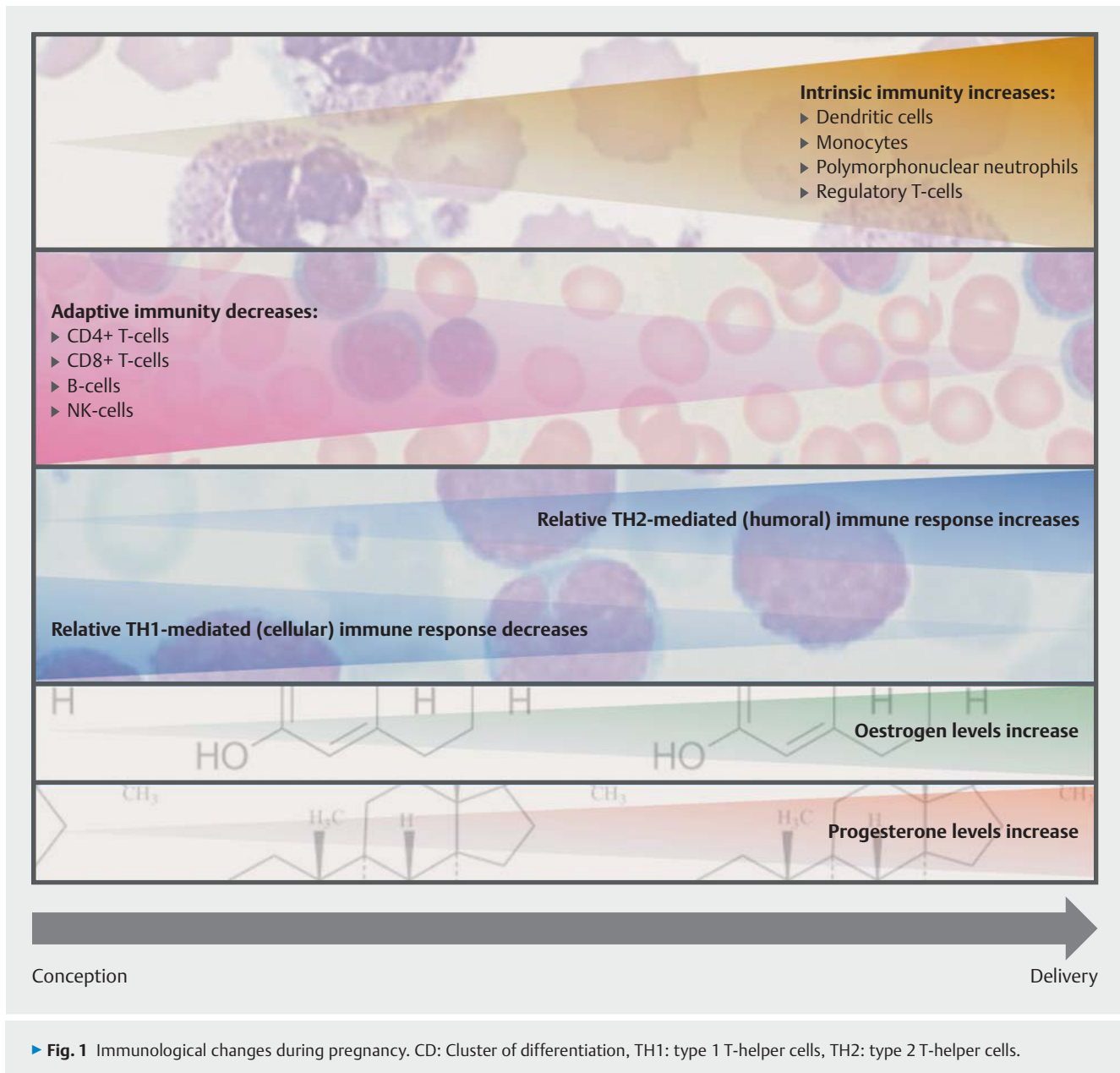n if these changes are complex and have not been fully elucidated yet, it can be assumed that the cellular arm of the immune system is suppressed, while the humoral component is augmented (so-called TH1-/TH2 phenotype shift). These effects increase as the pregnancy progresses [6, 8 – 10]. An overview of the immunological changes is provided in ▶ **Fig. 1**.

From a clinical perspective, a decreased cellular immunity during pregnancy is supported in particular by two observations: on the one hand, the severity of viral and fungal infections of the respiratory tract increases, especially in the second half of pregnancy [11 – 13]. In this context, the risk of reactivation of a latent tuberculosis infection also appears to be increased [14]. On the other hand, some autoimmune disorders, which are associated in particular with disorders of cellular immunity (e.g. rheumatoid arthritis or multiple sclerosis) frequently demonstrate a – partly marked – tendency to improve during pregnancy [8, 15]. Autoimmune disorders, however, which depend principally on the humoral immunity (e.g. systemic lupus erythematosus), are frequently associated with acute phases and an increased disease activity, especially towards the end of pregnancy [15].

In order for the immune system to be able to fight Mycobacterium tuberculosis (Mtb), the above changes that occur during pregnancy are relevant especially because a cellular immune response (T-helper cells) is so crucial. After ingestion via the respiratory tract, Mtb is internalised by macrophages, which then present the correspondingly processed antigens to the T-helper cells. This leads to a release of different cytokines (including tumour necrosis factor [TNF] and interferon-[IFN-]γ) and, ultimately, to granuloma formation. While the typical granulomas limit the inflammatory process on the one hand, they also create an environment that promotes the survival of the mycobacteria on the other hand [16, 17]. The persistence of mycobacteria in granulomas without a disease outbreak or after a past tuberculosis infection is referred to as a latent tuberculosis infection. In addition to other factors, TNF plays a crucial role in maintaining the granulomas [18, 19]. This observation is emphasised by the fact that the therapeutic use of TNF inhibitors (e.g. adalimumab) in autoimmune disorders increases the risk of reactivating a tuberculosis infection by a factor of 2–6 [20]. On the whole, it is assumed that there is an increased risk of progression or reactivation of a latent tuberculosis infection to manifest tuberculosis in pregnant women owing to the changes outlined above [21, 22].

Clinical findings, diagnostics and treatment of tuberculosis in pregnancy

Whenever the cardinal symptoms of TB are present in a patient (cough > 2 weeks, fever, nocturnal sweating and unwanted weight loss), tuberculosis should always be considered. The diagnosis is

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> ▶ **Fig. 1** Immunological changes during pregnancy. CD: Cluster of differentiation, TH1: type 1 T-helper cells, TH2: type 2 T-helper cells.

particularly difficult to establish in immunocompromised patients; they frequently exhibit atypical clinical findings (e.g. ascites or cerebral symptoms), and classical signs in the chest X-ray may be missing despite an involvement of the lungs [23]. In addition, the risk of extrapulmonary tuberculosis with atypical symptoms is markedly increased in pregnant patients compared to non-pregnant patients [4, 24 – 26].

Most of the pregnancy-associated tuberculosis cases are only confirmed post partum [14], the latency period is up to 6 months [14, 22]. This is most likely caused by a delayed diagnosis and the described immunological changes that increase over the course of a pregnancy [22]. An older review which analysed published perinatal tuberculosis cases showed that more than 75% of the patients did not exhibit any symptoms suggestive of tuberculosis during their pregnancy [27]. The start of the therapy was delayed

by a median of 27 days, 38% of the patients died from the infection. It must however be noted that the review included only 29 patients in total and that, in one third of the patients (n = 11) the meninges were involved, which is associated with an increased lethality [27]. One important reason for the delayed diagnosis owing to the alleged lack of symptoms is the physiological changes that are associated with pregnancy. Weight loss caused by tuberculosis can, for example, be masked by pregnancy-related oedema or the increase in the abdominal circumference; fatigue or laboured breathing may be misinterpreted as physiological. There is a very cautious approach to using radiological diagnostics in pregnant women, often due to a fear of potential harmful effects on the foetus caused by the radiation.

A chest X-ray or a respective CT scan is important to confirm a suspected case of pulmonary tuberculosis. CT scans are contra-

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▶ **Table 1** Recommended therapy for pulmonary tuberculosis (according to Schaberg et al. [31]).

Initial therapy	Duration (months)	Maintenance therapy	Duration (months)
Manifest tuberculosis			
INH, RMP, PZA, ETB	2	INH, RMP	4
INH, RMP, EMB	2	INH, RMP	7
Latent tuberculosis infection			
INH daily	9	–	–
RMP daily	4	–	–
INH and RMP daily	3–4	–	–
INH/Rifapentine weekly[1]	3	–	–

[1] not yet authorised in Germany

▶ **Table 2** Dosage recommendations for standard therapy (from: Schaberg et al. 2016 [31]).

Drug	Dose[1] (mg/kg body weight)	Dose range (mg/kg body weight)	Minimum/maximum dose (mg)	Standard dose (70 kg body weight)
Isoniazid	5	4–6	200/300	300
Rifampicin	10	8–12[3]	450/600	600
Pyrazinamide	25	20–30	1500/2500	1750
Ethambutol	15[2]	15–20	800/1600	1200

[1] Note dose adjustments for increasing body weight during the course of treatment.

[2] The optimal dose is not known. Ophthalmological complications, however, are less common at the indicated doses than at higher doses.

[3] Higher doses are being studied.

indicated in pregnancy; however, one single X-ray image in patients in whom there is reasonable suspicion (e.g. persistent cough) can be performed without a risk to the foetus [28] and is recommended in Germany whenever corresponding symptoms are present [29].

While microscopic analysis of the sputum is routinely used in countries with a high disease burden in spite of its low sensitivity (about 50%) [30], mycobacterial culturing is still considered the gold standard for confirming the diagnosis. However, the practical benefit of this method is limited by the long culturing times. In the past decade, rapid procedures have become available which are based on DNA amplification of the pathogen and which are recommended as a confirmatory assay by the WHO. These tests can include concurrent resistance testing for rifampicin and only take around 90 minutes to complete [31, 32]. A timely diagnosis is particularly important during pregnancy, as studies have shown an improved outcome for mothers and children when treatment was already initiated during pregnancy [25, 26, 33]. As long as open pulmonary tuberculosis is not ruled out, the patient must be adequately isolated [34].

Under no circumstances should the treatment be delayed. The standard therapy with a four-drug combination of ethambutol (ETB), isoniazid (INH), pyrazinamide (PZA) and rifampicin (RMP) for 2 months, followed by a two-drug combination of INH and RMP for 4 months, is also recommended for pregnant women [35]. The duration of therapy increases for extrapulmonary tuber-

culosis (e.g. 2 + 7 months for bone tuberculosis, 2 + 10 months for cerebral involvement) [35]. Alternative therapeutic regimens are illustrated in ▶ **Table 1**, dosage recommendations in ▶ **Table 2**.

The first-line therapeutic drugs listed above are deemed safe and are not associated with negative effects on the pregnancy. While most of the international societies – including those in Germany – also recommend PZA [35], the American Thoracic Society sees the use of this drug during pregnancy as critical owing to a lack of data on the teratogenicity [36]. If PZA is not used, the duration of therapy is extended to a total of 9 months (INH, RMP and EMB for 2 months, INH and RMP for 7 months) [35]. All pregnant and breastfeeding patients who are prescribed INH should also be prescribed vitamin B_6 (pyridoxine); combination drugs are available.

Even if a meta-analysis of 35 studies, published in 2014, on the treatment of tuberculosis in pregnancy showed no adverse effects of a second-line therapy on the mother or foetus [37], whenever resistant strains are present (so-called multi-drug resistance) the patients should only be treated in consultation with infectiologists and microbiologists taking into account the individual risks (tuberculosis vs. adverse drugs reactions). ▶ **Table 3** provides an overview of the individual second-line therapeutic drugs and their potentially harmful effects on the foetus.

Generally speaking, the response to therapy is also good in pregnancy. According to the results of a meta-analysis, nearly 89% of pregnant women can be treated successfully (culture conversion) [37].

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Tuberculosis and maternal mortality

Compared to pregnant women who do not suffer from tuberculosis, pregnant women with tuberculosis and their children have a poorer outcome in many areas. A recently published meta-analysis from Great Britain (13 studies, 3384 pregnant tuberculosis patients vs. 119 448 pregnant women without tuberculosis) showed an increased maternal risk, e.g. for anaemia (odds ratio [OR] 3.9) or for caesarean delivery (OR 2.1) [38]. Another study concluded that the maternal mortality is increased six-fold [4].

There is also a special risk in mothers co-infected with HIV; in these patients, the mortality is markedly increased [39, 40]. According to the results of a prospective cohort study (n = 88 pregnant women co-infected with HIV/tuberculosis vs. 155 pregnant women with HIV), the duration of hospitalisation and the risk or pre-eclampsia is also increased in this case [41].

The fact that there is not only a high proportion of extrapulmonary involvement in pregnant women (50–69% [4, 24–26]), but that this also tends to be associated with a poorer outcome, is also important, even if the figures are not statistically significant [38]. Cases with cerebral involvement may possibly be of crucial importance here. An older study on extrapulmonary courses also showed higher antenatal hospitalisation rates; this does not appear to be the case for tuberculous lymphadenitis [42].

Impact of maternal tuberculosis on the child and postnatal management of the newborn

For infants of mothers with tuberculosis, the probability of a low birth weight (OR 1.7), birth asphyxia (OR 4.6) or even perinatal death (OR 4.2) is markedly increased [38]. Antenatal infection of the foetus (congenital tuberculosis) is very rare according to the currently available data. For example, in a systematic review, only 170 cases of congenital tuberculosis are reported in the international literature between 1946 and 2009 [43]. In most cases, the mother was only diagnosed with tuberculosis after parturition. Purely extrapulmonary maternal disease courses are also associated with negative effects for newborn infants, e.g. a low birth weight or low APGAR scores [42].

In cases of antenatal infection, an infant mortality of 46% was reported in an old case series [44]; the more recent study of Peng et al. also assumes a mortality of around 40% in cases from 1994 onwards [43]. Diagnosing congenital tuberculosis is often difficult, as symptoms only appear after 2–3 weeks in most cases. Typical symptoms include fever, shortness of breath, hepato(spleno)-megaly and cough; in many cases, a bacterial or viral infection is suspected at first [43].

If maternal tuberculosis is diagnosed or suspected during pregnancy, the German Society of Pediatric Infectiology (DGPI) recommends always collecting fixed and native placental tissue samples for a histological and microbiological analysis after the delivery. Further diagnostics in the newborn are mandatory in these cases. Because prompt initiation of anti-tuberculosis therapy is of crucial importance and anti-tuberculosis four-drug therapy should be initiated whenever TB is suspected [45].

Asymptomatic newborns with relevant tuberculosis exposure should receive prophylactic therapy with INH and pyridoxine [45].

▶ Table 3 Second-line therapy for the treatment of tuberculosis in pregnancy (from: Schaberg et al. 2016 [31]).

Drug	Foetotoxicity	Terato-genicity
Gatifloxacin	unlikely	unlikely
Levofloxacin	unlikely	unlikely
Moxifloxacin	unlikely	unlikely
Amikacin	ototoxicity	unclear
Capreomycin	ototoxicity	yes (A)
Streptomycin	ototoxicity	no
Clofazimine	reversible skin discolouration	no
Cycloserine	postpartum sideroblastic anaemia	no
Terizidone	unclear	unclear
Ethionamide/ protionamide	delayed development	yes
Linezolid	unclear	no
Ethambutol	no	no
Pyrazinamide	rarely: jaundice	unclear
High-dose isoniazid	rarely: CNS damage, if pyridoxine supplementation is forgone	no
Bedaquilin	unclear	no
Delamanid	unclear	yes (A)
Para-amino-salicylic acid	postpartum diarrhoea	yes (first trimester)
Amoxicillin/ clavulanic acid	rarely: necrotic enterocolitis post partum	no
Meropenem/ imipenem	unclear	no

A: Animal study

Mothers can also be encouraged post partum to breastfeed the infant even if they are receiving anti-tuberculosis therapy, provided there is no risk of infecting the infant. This is the case when:

1. there is no infectious pulmonary tuberculosis in the mother (at least three negative sputa after starting therapy, alternatively anti-tuberculosis therapy for drug-susceptible tuberculosis > 21 days),
2. there are no clinical signs of tuberculous mastitis, and
3. adequate prophylactic therapy of the newborn was initiated [45].

If this does not apply or if there is any uncertainty, separation of the mother and child must be considered, whereby the mother and child can come together for breastfeeding under the condition that an FFP2 (Filtering-Face-Piece-2) mask is consistently used. These types of face masks filter at least 96% of all airborne particles measuring up to 6 µm, so that adequate protection can be assumed. An infection of the newborn via breast milk, even expressed milk, is unlikely. An anti-tuberculosis therapy of the mother is safe for the newborn, as only minor quantities of the first-line

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therapeutic drugs which are not toxic for the breastfed infant pass into breast milk [35, 36].

Prevention

A latent tuberculosis infection still presents challenges in routine clinical practice. A TB infection is defined as latent if no manifest disease develops after a primary infection, but the pathogens are still present in the host. Tests that can be used to detect the presence of pathogens include IFN-γ release assays (IGRA) (e.g. QuantiFERON test) or the classic tuberculin skin test (TST, also known as the Mendel-Mantoux test), which is also safe during pregnancy [29]. There is no concrete information on the sensitivity and specificity of TST and IGRA testing in pregnancy. However, it is generally assumed that the IGRA has a slightly higher specificity than the TST in regions with a low tuberculosis incidence, with otherwise comparable sensitivity, while the IGRA has a higher sensitivity in regions with a high tuberculosis incidence [46 – 48].

At the present time there are no international recommendations regarding screening for a latent tuberculosis infection in pregnant patients, also not in countries with a high disease burden. However, and as previously described, it is assumed that pregnant women are at an increased risk of progression or reactivation of a latent tuberculosis infection all the way to a manifest and potentially contagious disease. For this reason, the German Central Committee Against Tuberculosis (DZK), in collaboration with the German Society of Gynecology and Obstetrics (DGGG), generally recommends preferably using an IGRA for screening in pregnant, asylum-seeking women [29]. In case of a positive test result, this should in any case be followed by a chest X-ray.

If the IGRA or TST is positive, but there are no clinical signs of tuberculosis, treatment should in principle be considered if the patient recently had contact to a contagious index case or if an HIV infection is present [35]. Based on more recent findings, for example, rifampicin can be administered as monotherapy for 4 months [49] or INH as monotherapy for 9 months, combined with pyridoxine [50]. If the risk factors listed above (close contact to an index case, HIV infection) do not apply, a delay in the treatment to 2–3 months post partum can be considered [35].

A current analysis of the data of two randomised studies on the treatment of latent tuberculosis showed a rate that was similar to the general population of abortions and congenital abnormalities in pregnant tuberculosis patients who had been inadvertently exposed to at least one dose of INH monotherapy or INH + rifapentine [51].

Unfortunately, three American studies on the treatment of latent tuberculosis with INH during pregnancy reported poor adherence, with maximum completion rates of 21% [52 – 54]. The authors attributed this to side effects, among other things, but also to socioeconomic reasons [54]. Adherence was significantly improved if the patients received care from the same physician both ante partum and post partum [53].

Summary

The relevance of tuberculosis in pregnancy is highly likely to increase in Germany. Establishing the diagnosis can be made difficult by the changes in the physiology and immune system associated with pregnancy. The decrease in cellular immunity may also precipitate a less favourable course of a tuberculosis infection. For this reason, it is important to consider tuberculosis as a possible diagnosis and to initiate the corresponding diagnostic test battery in the presence of suggestive symptoms. In cases with reasonable clinical suspicion, the patient should be kept under aerogenic isolation until open pulmonary tuberculosis is ruled out. The drugs of choice include the common first-line therapeutic drugs whose use in pregnancy is considered safe and is recommended by the international societies. Latent tuberculosis is more challenging; only limited data are available for this type of infection. If there is reasonable suspicion, an IGRA should preferably be carried out. Based on the available data, treatment is recommended whenever risk factors are present. In newborn infants of mothers with perinatal tuberculosis, further diagnostics should be carried out to rule out congenital tuberculosis; diagnostics include the analysis of placental tissue. Due to the high neonatal mortality, treatment should also be initiated on sole suspicion of congenital tuberculosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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