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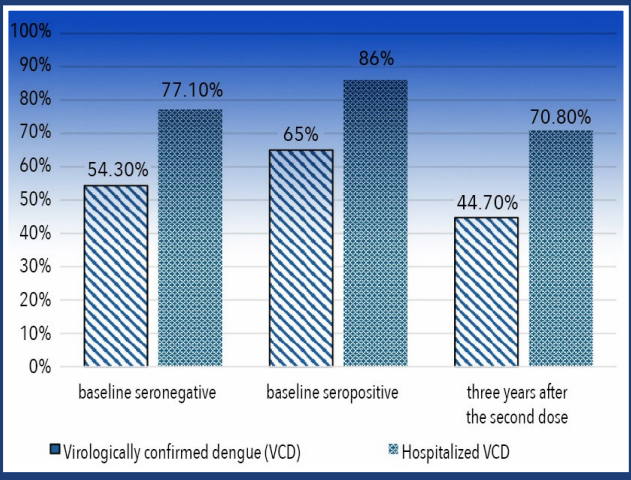

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Table of contents

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REVIEW PAPER

Fertility after methotrexate treatment for ectopic pregnancy: a narrative review

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Abstract

Background: Ectopic pregnancy (EP) occurs in up to 2% of all pregnancies, and its most common location is the fallopian tube. Treatment options include methotrexate (MTX), surgery and expectant management.
Material and methods: This review synthesizes the most important studies investigating the effect of MTX therapy for EP on subsequent female fertility.
Results: MTX treatment for EP does not seem to influence ovarian reserve. There are few studies and multiple discrepancies regarding tubal patency after MTX treatment. The pooled long-term rate of intrauterine pregnancies after MTX treatment was 69.6%, and of recurrent EP, 10.1%. MTX administered for EP treatment has a similar or better effect on subsequent fertility compared to surgery or expectant management.
Conclusions: MTX administration for EP gives equal or better outcomes in terms of subsequent fertility compared to other treatment methods. However, the chances of pregnancy are lower than in the general population. Due to the small number of RCTs and studies with long-term follow-up, future research is needed to provide definitive conclusions.
Keywords: methotrexate, fertility, ectopic pregnancy, pregnancy, birth rate

Introduction

Ectopic pregnancy (EP) occurs when a developing blastocyst implants outside of the uterine cavity. EP affects 1–2% of pregnancies. The most common location of EP is the fallopian tube (95%). Other positions include interstitial 2–4%, ovarian 3%, cervical 1%, or heterotopic 1–3% (concurrent

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presence of intrauterine and ectopic pregnancy) [1]. EP is responsible for 3–10% of pregnancy-related deaths, with the mortality rate remaining relatively stable over the years [1–3].

The combination of advanced ultrasound imaging and serial measurements of serum beta-human chorionic gonadotropin (b-hCG) allows 95–99% of cases of EP to be diagnosed [4]. Other biomarkers, such as activin-A, activin-B, activin-AB, follistatin, disintegrin and metalloprotease protein-12 (ADAM-12), Pregnancy-Associated Plasma Protein A (PAPP-A), Vascular Endothelial Growth Factor A (VEGF-A), Placental Growth Factor (PIGF), miRNAs, pregnancy-specific beta-1-glycoprotein 9 (PSG9), 3 (PSG3) and 11 (PSG11), heat-shock proteins 10 (HSP-10) and 27 (HSP-27), are the subject of intense research since their serum levels may help to distinguish a tubal EP from an early intrauterine pregnancy (IUP), or to predict EP treatment success [5–13].

There are several treatment options depending on the symptoms, the general condition, the b-hCG serum level, the presence of a viable embryo, and the diameter of the gestational sac [14]. In stable patients, non-symptomatic ones or those with mild symptoms, methotrexate (MTX) administration is a widely recognized and safe method. MTX in the treatment of EP can be administered intravenously or intramuscularly, using a one- or multi-dose protocol [1,15]. Medical treatment with MTX has good outcomes in cases of small masses (up to 3.5–4 cm), the absence of a foetal heart rate and/or relatively low b-hCG levels (up to 5000 mIU/ml) [16–18]. In patients with larger masses or very high b-hCG levels, surgical treatment with salpingostomy or salpingectomy might be needed. Surgical management is the treatment of choice in unstable patients, after ineffective MTX therapy, in women with ovarian pregnancy or those who do not accept other methods (MTX or expectant approach), or a prolonged stay in hospital, as in the case of MTX administration for tubal EP [19,20]. There are no treatment guidelines for interstitial EP or cervical pregnancy: they can be treated by administering MTX (sometimes directly into the gestational sac), surgery, or a combination of both [21–26]. The expectant approach can have a high success rate in women with tubal EP and low serum hCG levels [4,27–29].

EP is not only a life-threatening condition, but it can also affect the subsequent fertility of women trying to conceive. According to studies with long follow-up, previous EP increases the risk of recurrent EP up to 18.5% [30,31]. A large study based on the Danish national registry with follow-up of over 30 years shows that EP in the first pregnancy increases risk of further EP 4.7 times, and that EP in the first pregnancy reduces the subsequent birth rate compared to women with a normal first pregnancy, first pregnancy with a miscarriage, with an induced abortion or no previous pregnancy [32].

One of the possible mechanisms of compromised fertility after EP might be related to the chosen treatment. However, the data currently available do not provide a unanimous conclusion about the influence of medical and surgical treatment of EP on subsequent fertility. This review focuses on synthesizing data on the impact of MTX therapy for EP on subsequent fertility, with special consideration for spontaneous intrauterine pregnancy and/or birth rates.

MTX vs pregnancy: risks and timing

MTX is an antimetabolite of folic acid with proven teratogenic activity in humans and other mammals [33,34]. In the case of foetal exposure to MTX in the period of organogenesis, it can cause skull anomalies, facial dysmorphisms, cleft palate, limb abnormalities, cardiac malformations, and encephalic or neural tube defects [35]. The elimination half-life of MTX is 3–15 hours, depending on the dose, and 90% of its metabolites are eliminated in urine within 24 hours [36]. Some sources indicated the presence of MTX in liver tissues 116 days after exposure [37]. On the basis of reported MTX embryopathy and teratogenic effects of MTX in animal models, the manufacturers and scientific societies recommend avoiding pregnancy during and up to six months after exposure to MTX [16,34,38]. However, pregnancies with low rates of miscarriage or other complications have also been reported in women who conceived while receiving treatment with MTX [39–42]. Similarly, reassuring results were reported in women who became pregnant shortly after treatment of EP with MTX [43]. The authors compared foetal malformation and adverse outcome rates in pregnancies that occurred within the first six months after the last MTX treatment, and concluded that the time interval since the last MTX treatment had no effect on the outcome of the pregnancy that followed it.

MTX in the treatment of EP: influence on ovarian reserve

Most published data indicate that MTX used as a treatment for EP does not influence ovarian reserve measured in the levels of follicle-stimulating hormone (FSH) and antral follicle count (AFC), independently of the number of administered doses [44–46]. The study by Zargar et al. reported that MTX administration had no negative impact on ovarian reserve measured in levels of FSH, anti-müllerian hormone (AMH), and AFC eight weeks after the last dose of MTX [47]. Sahin et al. demonstrated that neither MTX nor MTX in association with salpingectomy affected AMH level three months after treatment of EP, although there was a temporary AMH decrease at one month in patients undergoing combined medical and surgical treatment [46]. Another recent study showed that there were no significant changes in

AMH levels one week after EP treatment with MTX compared to pre-treatment levels, both in single- and multi-dose groups [48]. Despite no significant change observed in AMH in the whole cohort within three to six months after MTX administration, the study by Çetin et al. also analyzed separately those patients with an increase vs a decrease in serum AMH level in the same time interval [49]. In both groups, the mean AMH change from pre- to post-treatment level was statistically significant. Moreover, the group exhibiting AMH increase comprised significantly more patients with a history of polycystic ovary syndrome (PCOS) and with a polycystic ovary morphology in the ultrasound. This raises the question of the effects of MTX on ovarian reserve in the general population. Therefore, in future studies it might be beneficial to analyze the influence of MTX on ovarian reserve independently for patients with and without PCOS.

MTX in the treatment of EP: influence on tubal patency

Patent tubes and ovarian reserve are important factors determining the success of future pregnancies. The mechanism in which MTX could influence tubal patency is unclear. Nevertheless, tubal patency after treatment of EP with MTX has been examined in multiple studies. A recent meta-analysis by Long et al. includes two randomized clinical trials (RCTs) comparing tubal patency after salpingostomy versus single-dose MTX for tubal EP [50–52]. It concluded that there was no difference between the two treatments. Tubal patency rates after MTX were 55% (23/42 patients) [52] and 65% (8/13 patients), respectively [50]. Another RCT by Khani et al. compared single-dose MTX, laparoscopic salpingostomy and open salpingostomy. Tubal patency rate was evaluated with hysterosalpingography at three months and was comparable between the treatments, with a rate of 91% in the MTX group (30/33 patients) [53]. A study by Melcer et al. used hysterosalpingo-foam sonography to evaluate tubal patency in patients with a history of MTX treatment for EP. It demonstrated a tubal patency rate of 60% (24/40 patients), with 15% presenting with hydrosalpinx and 25% with tube obstruction [54]. In the context of discrepancies in tubal patency rates, future studies are needed to provide a definitive conclusion.

MTX in the treatment of EP: future IUP and recurrent EP (REP)

Most studies that evaluate the effect of EP treatment on subsequent fertility compare surgical versus pharmacological treatments. In 2023, Hao et al. conducted a meta-analysis of 20 articles published between 1999 and 2022, with a total of 3530 women treated for EP, and 1023/3530 treated with MTX [55]. The primary outcomes of the study corresponded to the frequently

asked questions from the patients with EP: "Can I get pregnant successfully?" and "What is the risk of recurrence?". The follow-up period differed between these studies and ranged from 1 to15 years. Within this time period, 712 (69.6%) women conceived naturally and had an IUP. However, it should be taken into consideration that the follow-up times in some studies were relatively short (one year in three studies, one and a half years in two studies and two years in four studies), so the real rate of subsequent IUPs may be even higher. The pooled REP rate was 10.1% (75/739 patients).

As for the clinical studies that were not included in the this meta-analysis, Wyroba et al. reported that 61.5% (16/26) of patients who attempted to conceive after MTX treatment presented with successful pregnancy, resulting in live births and newborns with no congenital defects. The average time to pregnancy was 14.9 months (SD±10.9), with the first pregnancy after six months, which might be related to the received medical advice to avoid a pregnancy within three to six months after MTX treatment [56]. Reis et al. howed that 49.1% (79/161) of nulliparous patients treated with MTX gave birth within two years, and 6.8% (11/161) suffered from REP [57]. Khalil et al. reported that 54.5% of women got pregnant and gave birth to a healthy baby after MTX treatment, while 22.7% experienced a miscarriage and 13.6% an REP; the length of follow-up was not clearly reported [58]. The study by Mackenzie et al. reported follow-up data at 12 months from an RCT comparing MTX with gefitinib vs MTX with a placebo for EP treatment. Within this period, 53% (149/283) of women reported pregnancy; amongst them, 65% (93/142) delivered live babies, 40% (55/136) experienced a miscarriage and 17% (22/131), a REP [59].

MTX versus other treatments of EP

The meta-analysis by Hao et al. identified 20 studies that compared MTX and surgery, eight studies that compared MTX and salpingostomy, and six studies that compared MTX and salpingectomy [55]. They demonstrated that MTX treatment resulted in better subsequent fertility in terms of IUP rate when compared to surgery in general (OR=1.52, CI: 1.20–1.92), as well as when compared to salpingectomy (OR=1.61, 95% CI:1.52–2.93). However, there was no significant difference in IUP rate when comparing MTX and salpingostomy. As for the rate of subsequent REP, there was no significant difference in either of the comparisons. Therefore, Hao et al. concluded that future fertility after EP treatment is less compromised by pharmacological treatment than by surgery, and, if an operation is needed, salpingostomy is a better choice. It is also worth noting that the necessity of MTX use was not associated with worse subsequent fertility, since the odds of subsequent

IUP were similar in MTX and expectant management groups. A more recent study from 2024 described similar results, showing that in a two-year follow-up there was no significant difference in the rate of viable pregnancies between MTX and expectant management, but that there were significantly more pregnancies in the MTX group compared to the surgery group [60]. However, some studies report equally favourable outcomes of surgery and MTX in the treatment of EP. Dur et al. showed that both live birth (51.6% vs 44.6%) and REP (2.3% vs 1.4%) rates were not statistically different between the group treated with MTX versus the group treated with salpingectomy [61]. In the study by Alanwar et al., during the four-year follow-up, 62.5% (15/24) of patients treated with MTX presented with an intrauterine viable pregnancy, while in the case of those who had undergone surgery, this figure was 84.6% (22/26) (the difference was not statistically significant). REP occurred in 12.5% (3/24) of patients in the MTX group, and in none of the patients in the surgery group (the difference was not statistically significant) [62]. Finally, a study by Zieba et al. found similar live birth rates of 40–43.5% for patients treated previously with MTX, salpingotomy or salpingectomy, and a significantly better rate of 50% for patients treated with expectant management; however, this group comprised only eight patients and as such was much smaller than other treatment groups [19].

Conclusions

Contrary to previous beliefs, some clinical studies suggest that the time since the last MTX treatment of EP may have no effect on the outcomes of the subsequent pregnancy. EP treatment with MTX does not seem to influence the ovarian reserve, evaluated with FSH, AMH and AFC. However, future studies are needed to ensure a separate analysis for patients with normal versus polycystic ovarian morphology and function. There are few studies and multiple discrepancies regarding tubal patency after MTX treatment. Future studies are required to provide definitive conclusions. According to the literature, 84% of couples trying to conceive get pregnant within the first 12 months [(63]. Fertility after MTX treatment of EP was reported as a pooled 69.6% rate of IUP, according to a meta-analysis of over one thousand patients with follow-ups from 1 to 15 years [55]. In the same study, the pooled REP rate was 10.1%. Not taking into consideration the patients' procreative plans (in other words, including the patients who are not trying to conceive) and reporting outcomes from short follow-ups may provide a false image of birth rates after MTX treatment. MTX administered for EP treatment has a similar or better effect on subsequent fertility compared to surgery or expectant management.

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REVIEW PAPER

Advancing Keratoconus Treatment. The Promise of Theranostic Technology

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Abstract

Background: Keratoconus (KC), a progressive ectatic disorder of the cornea, presents significant challenges in clinical management due to its unpredictable progression and individualized nature. Advances in treatment modalities, particularly corneal cross-linking (CXL), have revolutionized the ability to halt disease progression. Yet, a significant gap remains in achieving personalized, outcome-driven interventions.
Material and methods: Literature review.
Results: New personalized CXL approach based on theranostic biomarkers proved safe and effective in the treatment of KC and offers personalized approach to treat the disease.
Conclusions: Theranostics technology integrated with advanced UV-A device for CXL procedure permits to deliver the precise therapeutical dose of riboflavin and personalized UV-A light amount for the photo-activation in the cornea. This real-time monitoring of riboflavin concentration in the cornea during CXL procedure permits to obtain better predictability of the final outcome on personal basis.
Keywords: corneal cross-linking, keratoconus, theranostic

Introduction

Keratoconus (KC) is a corneal disease characterized by progressive ectasia with corneal thinning and steepening. It can cause a visual impairment that in severe forms, especially in young patients, requires corneal transplantation. Clinical signs of KC manifest frequently at puberty when the progression is more aggressive compared to adult onset, as the disease

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usually halts in the fourth decade of life. Disease prevalence depends on the geographical location, reaching 5% in the Middle East [1–4].

Corneal cross-linking (CXL) based on riboflavin/UV-A interaction is a well-established procedure worldwide that induces corneal stiffening and is used to slow down or halt KC progression. Riboflavin exhibits photosensitizing properties in the presence of UV-A light and reacts with a wide range of electron-donating substrates through photochemical mechanisms. The main mechanism of the riboflavin/ UV-A CXL procedure relies on the direct interaction between riboflavin triplets and reactive groups of stromal proteins which induce the cross-linking of the proteins through radical reactions [5–7].

Several CXL protocols have been clinically validated for the treatment of keratoconus. They differ in the type and time of riboflavin application and UV-A irradiance treatment settings. The first CXL protocol, the so-called Dresden protocol, provides for the removal of the corneal epithelium and administration of a dextran-enriched riboflavin ophthalmic solution on to the corneal stroma for 30 min. Subsequently, the cornea is irradiated by a UV-A light device with 3 mW/cm power density for 30 min. to obtain a total delivered energy density of 5.4 J/cm^2. In the past decade, different UV-A treatment protocols have been developed and validated in the clinic [8–11]. At the same time, different riboflavin ophthalmic solutions have been used with their higher benefit/safety profile assessment based on pre-clinical and clinical evidence [12,13]. Nevertheless, the CXL treatment proved to be a valid therapy that reduced significantly the number of keratoplasties in patients with KC [8,14]. According to scientific evidence, the efficacy of the procedure shows a huge variation. CXL with epithelial removal is considered the most effective so far, but it represents the primary predisposing factor for major complications. In fact, adverse effects of the epithelium-off protocol include ocular pain, transient corneal oedema and corneal haze, and in some cases severe events, such as corneal infections, melting and corneal scarring with vision loss [15–17]. Several treatment protocols without epithelium removal, so called epithelium-on, have been developed in order to minimize these complications, although their clinical efficacy still remains an object of debate [9,18–21]. Nowadays, transepithelial CXL treatment protocol remains challenging since it is difficult to understand the real amount of the riboflavin penetrating into the corneal stroma through the intact epithelium.

Thus, it is evident that a precise knowledge of the principles of UV-A light/riboflavin interaction with the cornea could prove fundamental in improving the therapeutic management of keratoconus with CXL

[22]. Mathematical models and experimental studies have supported the hypothesis that the concentration of riboflavin in the cornea before UV-A light irradiation is the most important variable influencing the therapeutic effect of CXL treatment [22–23].

Recently, theranostic-guided corneal cross-linking using a theranostic UV-A medical device has been made available for treating keratoconus. Theranostic technology, a revolutionary approach combining therapy with diagnostic capabilities, is poised to address this gap by enabling precise, predictable, and personalized treatments for keratoconus.

What is Theranostic Technology?

Theranostics is an emerging and innovative therapeutic paradigm for precise and personalized medicine. Theranostics integrates therapeutic intervention with real-time diagnostics to optimize treatment strategies. Theranostic technology integrated with an advanced UV-A device for CXL enables the precise therapeutic dose of riboflavin and its UV-A light photo-activation to be customized to the individual cornea. The purpose of this real-time monitoring of corneal riboflavin concentration on a personal basis is to improve the predictability of clinical outcomes and to minimize risks of adverse events.

In the context of keratoconus, theranostic technology is embodied in a UV-A light device that utilizes feedback-driven algorithms to guide corneal cross-linking. This innovative system employs advanced imaging and predictive modelling to monitor corneal response to UV-A exposure during the procedure.

The theranostic UV device works by first capturing the corneal topography and wavefront aberrations in high resolution. These diagnostic measurements are used to model the biomechanical properties of the cornea and predict its response to UV-A irradiation. During treatment, the device continuously adjusts UV-A light delivery on the basis of real-time feedback, ensuring a precise reshaping of the cornea's curvature while minimizing collateral tissue damage. By tailoring the treatment parameters to the individual's unique corneal anatomy and biomechanical profile, theranostics not only enhances the safety and efficacy of the procedure but also allows clinical outcomes to be predicted with unparalleled accuracy (Figure 1).

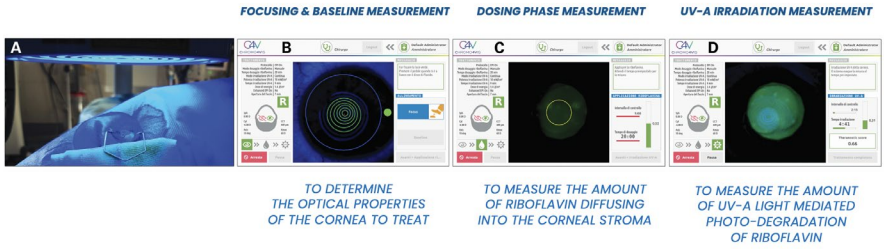

Figure 1. Theranostic device (A). Focusing and baseline measurement (B). Measure of riboflavin amount during soaking (C). Measurement of riboflavin amount during cross-linking process (D)

The ARGO Trial: Validating Precision in Predictive Keratoconus Treatment

The ARGO trial, a landmark study published in *Ophthalmology*, provides robust evidence supporting the efficacy and predictive capabilities of theranostic-guided corneal cross-linking. This multicentre, prospective clinical trial enrolled patients with progressive keratoconus to evaluate the technology's ability to achieve predictable and consistent treatment outcomes [24].

Key findings from the ARGO trial include:

1. Predictive Accuracy: The trial demonstrated a 91% accuracy rate in predicting the flattening of the maximum keratometry (Kmax) value at the 1-year follow-up. This level of precision highlights the reliability of the device's predictive algorithms in guiding treatment.
2. Treatment Precision: The theranostic-guided UV-A system achieved 95% precision in delivering the intended Kmax flattening, underscoring its ability to adhere to personalized treatment goals.
3. Clinical Outcomes: Patients experienced significant and consistent improvements in corneal curvature, with minimal adverse effects. The reduction in higher-order aberrations further contributed to enhanced visual quality.

These results mark a paradigm shift in keratoconus management, establishing theranostics as a cornerstone for precise and personalized interventions.

Expanding the Horizons: New Opportunities in Keratoconus Treatment

The success of theranostic-guided UV-A treatment opens up new avenues for advancing keratoconus care. Beyond its proven efficacy in halting disease progression, the technology paves the way for transformative applications:

1. Enhanced Early Diagnosis and Monitoring
   Theranostics enables the integration of diagnostic and therapeutic workflows, allowing clinicians to identify keratoconus at its earliest stages. Early detection, combined with predictive modelling, facilitates timely intervention to prevent significant visual deterioration.
2. Customizable Treatment Protocols
   By leveraging individualized corneal biomechanics and topography, theranostics allows for the development of customized treatment protocols. This adaptability ensures that patients with varying disease severities and anatomical variations receive optimal care.
3. Application in Other Corneal Disorders
   The principles of theranostics are not confined to keratoconus alone. The technology's potential extends to other corneal conditions, such as pellucid marginal degeneration and post-refractive surgery ectasia, where precise biomechanical modulation is critical.
4. Integration with Artificial Intelligence (AI)
   The future of theranostics lies in its synergy with AI-driven algorithms. Machine learning can enhance the predictive accuracy of theranostic devices by analyzing vast datasets of corneal response patterns. This integration will further refine treatment protocols and improve patient outcomes.
5. Development of Patterned UV-A Treatments
   Research is already underway to explore patterned theranostic-guided UV-A treatments. This approach aims to selectively target specific corneal regions for cross-linking, offering a more nuanced and effective solution for irregular astigmatism and advanced keratoconus cases.

Challenges and Future Directions

While theranostics represents a significant advancement in keratoconus treatment, challenges remain in its widespread adoption. The technology's complexity necessitates specialized training for clinicians, and its integration into clinical practice requires robust infrastructure and regulatory approvals. Additionally, cost considerations may pose barriers to accessibility, particularly in resource-limited settings.

Future research should focus on addressing these challenges through the development of cost-effective devices, streamlined training programs, and expanded clinical trials to validate the technology across diverse patient populations. Collaboration between industry leaders, academic institutions, and regulatory bodies will be essential to drive innovation and ensure equitable access to theranostic-guided treatments.

Conclusion

Theranostic technology heralds a new era in keratoconus management, offering a precise, predictive, and personalized approach to treatment. The validation provided by the ARGO trial underscores its potential to redefine clinical outcomes, enhancing both patient satisfaction and quality of life. As the field continues to evolve, theranostics is set to expand its impact, not only within ophthalmology but also as a model for integrating diagnostics and therapy across medical disciplines. By embracing this cutting-edge technology, clinicians and researchers have the opportunity to transform the standard of care for keratoconus and beyond.

Conflict of interest

Anna M Roszkowska no one, Marco Lombardo is co-inventor of the Patents IT102016000007349, EP3407920B1 and CN201680080266.9 for theranostic-guided corneal cross-linking.

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Diagnosing GERD: A Toolkit for the Modern Clinician

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a prevalent chronic gastrointestinal disorder causing significant symptoms and complications, with varying prevalence worldwide. It leads to substantial healthcare costs, particularly in the USA. Effective management relies on clear diagnostic evidence from endoscopy or reflux monitoring.
Material and methods: The Montreal Consensus defines GERD based on symptoms and complications. Diagnosis can be complex, requiring various tools. GERD is categorized into esophageal and extra-esophageal syndromes, influencing diagnostic and therapeutic strategies. The Polish Society of Gastroenterology emphasizes history, clinical symptoms, and empirical PPI tests, supported by endoscopy, manometry, and pH monitoring.
Results: Endoscopy is indicated for alarm symptoms or multiple risk factors, identifying hiatal hernias and esophageal inflammation. Manometry evaluates esophageal motor function before anti-reflux surgery, measuring LES pressure to exclude motility disorders. 24-hour pH monitoring with impedance is considered the gold standard in diagnosing GERD.
Conclusions: GERD diagnosis and management need symptom assessment, empirical testing, and specific diagnostics like endoscopy, manometry, and pH monitoring for accurate diagnosis and effective treatment. These approaches ensure tailored management and improved patient outcomes.
Keywords: GERD, reflux disease

Introduction

Gastroesophageal reflux disease (GERD) is a common, chronic condition of the digestive system, characterized by the reflux of the stomach contents into the oesophagus, leading to troublesome symptoms and/or complications. It is estimated that the prevalence of GERD in Europe ranges from 9% to 26%, in the USA it is around 18–28%, while in Asia about 5% of the adult population is affected. The prevalence varies depending on the region and

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the diagnostic definitions used [1]. GERD and oesophagitis are the second most common cause of outpatient visits after abdominal pain. Annual costs related to GERD in the United States are estimated at 15–20 billion dollars, with more than half of these costs spent on treatment. In the past five years, expenses on acid-suppressing drugs, used for various indications, have been estimated at approximately 60 billion dollars [2]. At the same time, it has been shown that about 30% of individuals using proton pump inhibitors (PPIs) do not have documented indications for their use [3].

Troublesome, typical symptoms of GERD may be sufficient to attempt treatment with acid-suppressing medications, but initial oesophageal examination is recommended for all other categories of symptoms (so-called atypical symptoms) and for patients who do not respond to PPIs, before using invasive GERD treatment methods or long-term pharmacological therapy. The modern approach to GERD management requires clear evidence of reflux-related pathology through endoscopy and/or abnormal reflux monitoring (using values specified by the Lyon Consensus) [4].

Diagnosis

According to the Montreal Consensus, GERD can be diagnosed on the basis of bothersome symptoms that negatively affect the quality of life, such as heartburn or regurgitation, or the presence of GERD complications. In the absence of these symptoms or typical complications, diagnosing GERD becomes complex and involves various diagnostic tools, each with its advantages and disadvantages. The Montreal Consensus distinguishes between oesophageal and extra-oesophageal syndromes of GERD. Oesophageal syndromes are further divided into symptomatic syndromes (where typical GERD symptoms occur) and syndromes associated with oesophageal injury (oesophagitis, Barrett's oesophagus [BE)]and oesophageal adenocarcinoma). Extra-oesophageal syndromes are categorized into those with a documented association with GERD (cough, laryngitis, bronchial asthma and dental erosions) and those with an unclear association (pharyngitis, recurrent otitis media, sinusitis and idiopathic pulmonary fibrosis) [5]. This classification determines the subsequent diagnostic and therapeutic approach for the patient.

According to the guidelines of the Polish Society of Gastroenterology (PTG-E), the diagnosis of GERD includes several key steps. A detailed medical history and clinical symptoms are fundamental: the presence of the aforementioned typical GERD symptoms is often sufficient for diagnosis, which is confirmed through empirical tests, i.e. PPI tests. Improvement of symptoms after PPI treatment can confirm the diagnosis of GERD. This

approach applies to oesophageal symptomatic syndromes without the presence of alarm symptoms (dysphagia, weight loss, bleeding, anemia) [5].

Diagnostic Tools

For other clinical scenarios, modern medicine offers a range of tests that support GERD diagnosis, especially in cases where there is no clear response to pharmacotherapy. The existence of a "gold standard" for GERD diagnosis had not been clearly defined until the Lyon Consensus [4].

Upper gastrointestinal endoscopy is not routinely recommended in the absence of alarm symptoms. Indications for the test include the presence of three or more risk factors, such as GERD duration >5 years, age ≥50 years, white race, male gender, obesity, Barrett's oesophagus, or a first-degree relative with oesophageal adenocarcinoma. Lack of response to pharmacological treatment is also an indication for the examination. During the procedure, features of hiatal hernia and inflammatory changes in the distal oesophagus, classified according to the Los Angeles classification, can be observed. Currently, grade B or higher confirms a GERD diagnosis. Routine biopsy of the distal oesophagus is not recommended due to method limitations. Patients should fast for at least six hours before the procedure [6].

Oesophageal manometry: This test evaluates oesophageal motor function, especially before planned anti-reflux surgery. It diagnoses motor disorders that may affect treatment and outcomes. In GERD diagnosis, it is mainly used to measure the lower oesophageal sphincter (LES) and exclude significant motor disorders. It is important to note that prior gastroscopy can affect the manometric results, complicating the diagnosis. Patients should fast for at least six hours or longer if achalasia is suspected [7].

24-hour multichannel intraluminal impedance-pH monitoring is the current standard for differentiating GERD from functional heartburn and reflux hypersensitivity, diagnosing GERD resistance to PPI treatment, and confirming or excluding extra-oesophageal syndromes, where it is considered the gold standard. It is also a predictor of the success of surgical anti-reflux treatment, which should be performed before such a procedure [8]. After identifying the LES, the catheter tip is placed 5 cm above the upper LES margin during the test. The standard probe has six to eight metal rings at various heights and one or two pH sensors. This structure allows the recording of electrical resistance between the rings, tracking the movement, direction, and nature of the bolus. It provides information on the type of reflux (acidic, weakly acidic, or non-acidic) and its form (liquid, mixed, or gaseous).

The test gives data on acid exposure time (AET), the number of reflux episodes, and various parameters like MNBI (mean nocturnal baseline impedance – values below 2292 Ω suggest significant mucosal damage supporting GERD diagnosis) or bolus exposure time. Furthermore, using mathematical algorithms, such as the symptom index (SI) and symptom association probability (SAP), it is possible to determine whether the patient's symptoms can be linked to reflux.

During diagnostics, laryngoscopy should not be overlooked, as it is increasingly used as an initial test for atypical extra-oesophageal symptoms, such as throat dryness, burning, foreign body sensation, chronic throat clearing, coughing, drooling, spasms, choking, frequent swallowing, belching, halitosis, otalgia, and nonspecific neck pain [9]. However, the presence of these symptoms alone should not form the basis for diagnosing GERD. The appearance of reflux laryngitis depends largely on the examiner's experience, and in many cases, GERD is overdiagnosed. Several interpretation scales have been developed, the most popular being the Reflux Finding Score (RFS) by Belafsky [10].

Conclusion

The high prevalence of GERD and its projected increase in the coming years necessitate improvement and wider access to diagnostic tools. Currently, no perfect test exists that can diagnose GERD with 100% sensitivity and specificity. Diagnosis should be based on medical history, risk factors, empirical treatment, endoscopic examination, and especially 24-hour pH monitoring with impedance to identify the largest possible group of patients with a high likelihood of developing GERD complications. GERD can significantly reduce the quality of life and lead to upper gastrointestinal bleeding, dysphagia from post-inflammatory strictures, and the development of adenocarcinoma based on Barrett's oesophagus.

Awareness of GERD and its complications in society is crucial, as is the need for basic diagnostic protocols in primary care and access to more advanced diagnostic tools.

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SHORT REPORT

TAK-003 dengue vaccine – a new hope for safe travel to endemic areas: efficacy, safety and future perspectives

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Abstract

Background: Dengue fever remains a major health risk, with 100 to 400 million clinical cases occurring each year. TAK-003 a tetravalent live-attenuated vaccine, offers potential protection against all four dengue virus (DENV) serotypes (DENV-1, DENV-2, DENV-3, DENV-4), providing a new option for travelers to dengue-endemic areas.
Material and methods: This paper examines the efficacy and safety of the TAK-003 dengue vaccine, with a focus on its potential to protect seronegative travelers visiting regions endemic to dengue. The analysis includes data from clinical trials assessing its performance in both seropositive and seronegative individuals, and its ability to prevent severe disease and hospitalizations.
Results: TAK-003 dengue vaccine has shown high efficacy against DENV-1 and DENV-2, while efficacy against DENV-3 was comparatively lower, particularly in seronegative individuals. The vaccine is generally well-tolerated, with mild side effects such as injection site pain and headaches. Importantly, it offers strong protection against severe dengue cases and hospitalizations, making it a valuable tool for travelers.
Conclusions: TAK-003 dengue vaccine provides high protection in dengue-endemic regions, particularly against DENV-1 and DENV-2. Protection is higher in seropositive individuals, likely due to prior infection. Vaccination is not recommended for travelers with no history of dengue fever. A booster dose study is under consideration.
Keywords: safety, vaccine, dengue fever, efficacy, TAK-003

Introduction

Global travel increases exposure to health risks, including dengue fever in endemic regions. The new TAK-003 vaccine offers travellers added protection against this mosquito-borne disease. TAK-003, a tetravalent live-attenuated vaccine, offers potential protection against all four dengue virus (DENV) serotypes (DENV-1, DENV-2, DENV-3, DENV-4) [2].

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Traditional prevention has relied on mosquito control and personal protection, although effectiveness is limited. The existing Dengvaxia® vaccine is limited to seropositive individuals, as seronegative vaccination may worsen dengue due to antibody-dependent enhancement, leading to more severe reinfection outcomes. During a mass Dengvaxia® campaign in the Philippines, 51 deaths were reported, primarily among seronegative children, most between 9 and 13 years of age, with 15 cases confirmed as dengue-related [3].

This report evaluates the TAK-003 dengue vaccine's potential as a standard health measure for tourists in endemic zones, assessing its efficacy and prospects for safer travel and protection against dengue fever.

Vaccine efficacy

Clinical trials were conducted in endemic countries (Brazil, Colombia, Nicaragua, Panama, the Philippines, Sri Lanka, the Dominican Republic, Thailand) in the 4–16 age group and non-endemic countries (the United States) in the 18–60 age group. The first dose of the vaccine was administered on day 0, and then the second dose after 90 days [4–6].

During the vaccine immunogenicity study, seropositivity rates in baseline seronegative individuals increased from 0% at the start of the study to between 94.6% and 100% on day 120 after vaccine injection. Seropositivity declined slightly by day 270 post-injection, but still remained at substantially high levels, ensuring efficacy. Clinical immunogenicity trials have confirmed that the TAK-003 vaccine is highly immunogenic against all four dengue serotypes in both adults and children, regardless of whether they have been previously exposed to the virus [4,5].

In people who are baseline seronegative (i.e., no previous contact with the dengue virus), the TAK-003 dengue vaccine provides protection primarily against serotypes DENV-1 and DENV-2, which are responsible for the most severe cases of dengue fever. In particular, DENV-2 often leads to hemorrhagic fever (HF). However, it is worth mentioning that the vaccine does not provide high protection against less common serotypes, such as DENV-3 and DENV-4.

In the long-term study, three years after two doses of TAK-003, the efficacy of the vaccine against hospitalized virologically confirmed dengue (VCD) remains high, providing solid protection against a severe clinical course and possible hospitalization. However the decline in efficacy against VCD observed in the long-term clinical studies suggests some reduction in protection against milder courses of infection (Figure 1).

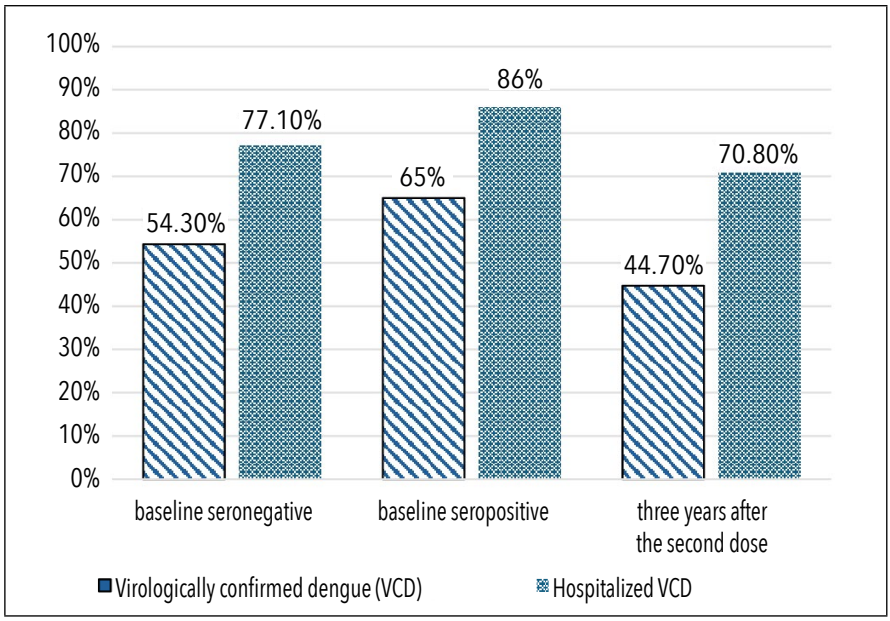

Figure 1. Efficacy of the TAK-003 dengue vaccine over time

Source: Figure created by the author, based on data from [5].

It is also worth noting that the vaccine's efficacy increases with age in children and adolescents. The results of one study suggest slightly lower cumulative vaccine efficacy in the youngest age group. In the 4–5 year age group, there was a decrease in efficacy from a result of 72.8% at one year post-vaccination to 24.5% at two years post-vaccination. In the older age groups, efficacy appeared to be higher after vaccination and showed a smaller decrease over time. In the 6–11 age group, efficacy was 80.7% after one year post-vaccination and decreased to 60.6% after two years. In the 12–16 age group, there was 83.3% efficacy after one year and 71.2% after two years post-vaccination [5,6].

Safety

Safety analyses conducted after administration of the vaccine showed no anaphylactic reactions associated with vaccination. Long-term observation after the vaccine for up to four weeks showed no serious adverse reactions or vaccine-related deaths during follow-up, which was carried out up to 36 months after the last dose [4,5,7].

No significant safety risks or concerns were identified according to gender, pre-vaccination serological status or age in the 4–60 age group.

However, local side effects, such as pain, redness and swelling at the injection site, were observed, which were mild and resolved rapidly (within one to three days). Systemic side effects mainly included headache and myalgia and resolved after three to four days. These symptoms occurred more frequently after the first dose, with a reduced number of reported cases after the second dose [8].

As it is a live vaccine, vaccination is contraindicated in pregnant or breastfeeding women, in immunosuppressed persons (including those with congenital immunodeficiencies and those undergoing immunosuppressive therapy), in people, who have received chemotherapy or high doses of systemic corticosteroids during the four weeks before vaccination, and in HIV-infected people with both symptomatic and asymptomatic impaired immune function [2].

Practical Tips for Travellers

The vaccine should be given in two doses, three months apart [2]. It is advisable to begin vaccination a few months before travel. In addition, other preventive measures, such as mosquito repellents, protective clothing and avoiding being outdoors during peak mosquito activity should be considered. In seropositive individuals only, the previous vaccine, Dengvaxia, should be explored in order to increase protection against dengue fever [1,3].

From a vaccination standpoint, there are various approaches to the issue, which depend on the committee (the UK, Germany and WHO respectively). The Joint Committee on Vaccination and Immunization (JCVI) and the Standing Committee on Vaccination (STIKO) do not recommend vaccination for those who have no history of dengue fever prior to travel. The Strategic Advisory Group of Experts on Immunization (SAGE) has highlighted the vaccine's lower efficacy in such individuals. The Swedish Society for Infectious Disease Physicians recommends that vaccination for dengue should be considered in the 4–16 age group, while above the age of 17 vaccination should only be considered for longer trips. There is no upper age restriction for the TAK-003 vaccine, and in the clinical trials there were no participants over 60 years of age [9–12].

However, the WHO has issued a recommendation regarding vaccinating children in the 6–16 age group with TAK-003 only in endemic countries with a high intensity of dengue virus transmission [1].

It is important to keep in mind that the vaccine primarily protects against severe forms of dengue and not necessarily against the infection itself, which is often asymptomatic [13] or mild. TAK-003 dengue effectively reduces the risk of hospitalization and severe cases of dengue fever [5,7,8],

which is an important concern, especially for older adults or those travelling to high-risk areas.

TAK-003 dengue vaccine can be given simultaneously with hepatitis A virus (HAV) and yellow fever vaccines. The results of the study showed that the combined administration of the vaccines does not reduce the effectiveness of any of the vaccines and has no impact on safety [14,15].

Conclusions

TAK-003 dengue vaccine provides a high level of protection to seropositive travellers in endemic countries. Studies have shown particularly high efficacy against serotypes DENV-1 and DENV-2, with lower efficacy against DENV-3. The vaccine has high efficacy that protects primarily against severe cases of dengue fever and the need for hospitalization. Vaccination of seronegative travellers should only be considered in the case of longer stays in endemic countries. The vaccine showed similarly high efficacy in every age group apart from the youngest 4–5 age group that participated in the clinical trial. However, they represented the smallest age group, making it difficult to draw firm conclusions. The vaccine demonstrates a strong safety profile, and adverse events, such as local pain at the injection site, are considered to be a natural reaction of the body to the needle injection. It is worth bearing in mind that the TAK-003 vaccine does not provide a high level of protection against serotype DENV-3 and DENV-4, and vaccine efficacy is lower in seronegative individuals. In dengue infection, antibody-dependent enhancement (ADE) may occur, increasing the risk of severe disease upon secondary infection with a different serotype. Further research is needed to investigate the possibility of a booster dose, which may increase the efficacy of the vaccine against less common serotypes and extend the duration of efficacy.

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