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Endometriosis and Artificial Intelligence: Advancing Women's Healthcare

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ABSTRACT

Endometriosis is a chronic disease characterized by an occurrence of endometrial-like tissue located outside of the uterus that can result in estrogen-driven inflammation. It significantly impacts the quality of life and productivity of affected individuals. The economic burden associated with endometriosis-related healthcare costs and productivity loss underscores the importance of early detection and management. Recent advancements in artificial intelligence (AI) offer promising avenues for improving endometriosis diagnosis and treatment. AI algorithms have been developed to analyze clinical data and predict the presence of endometriosis with high accuracy. Additionally, AI-driven approaches facilitate the identification of novel biomarkers and therapeutic targets, potentially revolutionizing personalized medicine in endometriosis management. Symptom tracking using wearable devices and smartphone apps provides valuable insights into disease progression and treatment response. However, challenges such as data variability, portability, and privacy must be addressed to ensure the reliability and ethical use of AI in endometriosis management. In conclusion, AI holds great promise in advancing the diagnosis, treatment, and management of endometriosis. By leveraging innovative technologies and interdisciplinary collaborations, AI has the potential to transform the landscape of women's health and usher in a new era of personalized medicine for endometriosis.

INTRODUCTION

Endometriosis is a chronic disease characterized by an occurrence of endometrial-like tissue located outside of the uterus that can result in estrogen-driven inflammation. It is a complex condition that has a significant influence on the quality of life of individuals affected and has no cure.[1] While endometriosis prevalence in women of reproductive age is often reported as 10%, figures from around the world vary greatly, with ranges of 2% to 45% for healthy women and 2% to 77% for infertile women.[2]

The anticipated yearly expenses for endometriosis-related healthcare and productivity loss are $2801 and $1023 for each patient, respectively. Medical professionals should be more aware of the illness, which should result in earlier detection, less suffering, and increased productivity.[3]

There are three different kinds of endometriosis: deep endometriosis, ovarian endometriosis, and superficial endometriosis. Based on the stage of the disease, the American Society and the American Fertility Society categorize endometriosis into four distinct types, ranging from "minimal" to "severe".[4]

- Stage 1 (mild disease): small areas of endometriosis.
- Stage 2 (moderate illness): More widespread and deeper
- Stage 3 (moderate disease): Small cysts present on one or both ovaries.
- Stage 4 (severe disease): Deeply impacted rectum, uterus, and peritoneum.

This disease's non-specific signs and symptoms might vary in intensity, leading to clinical heterogeneity and complicating the diagnosis. Depending on the type of endometriosis, the location of implants, the stage, and the severity of the condition, patients may present with a variety of symptoms, such as dysmenorrhea, dyspareunia, abdominal pain, severe pelvic pain, menorrhagia, bowel symptoms, urinary symptoms, and diminished fertility or infertility.[5]

Retrograde menstruation has been suggested to be a major cause of endometrial deposits, however, other factors such as endocrine and metabolic circumstances, epithelial-mesenchymal transition, and altered inflammatory and immune reactions in genetically vulnerable individuals all play a role.[6] However, retrograde menstruation does not account for the infrequent incidences of lesions of the endometrium in the urogenital tract. The benign metastasis theory postulates that endometrial tissue "spreads" to distant locations, including the brain, through blood or lymphatic veins. However, the theory is not supported by any

reliable data. In comparison to normal tissue, there is evidence of increased estrogen production by the stromal cells in the tissue of the endometrium. The main cause of elevated estrogen levels is the increased activity of the enzyme aromatase, which converts androgens into estrogen. heredity occurrence of this disease is supported by the associations between mutations in the PTEN and ARID1A genes.[7]

Many patients experience a great deal of delay in obtaining an endometriosis diagnosis due to a variety of factors, including non-specific symptoms, an extensive differential list, clinician ignorance, irrelevant investigations, and a lack of non-invasive techniques for diagnosis. The diagnosis duration spans 4 to 11 years, with 65% of women originally misdiagnosed.[8] The current delays in diagnosis have a greater impact on life than one might anticipate from rapid and efficient treatment.

In the past, a thorough history and physical examination were used to diagnose endometriosis. Hysterosalpingography, pelvic magnetic resonance imaging (MRI), or a barium enema are further screening procedures that may be taken into consideration. However, a definite diagnosis is made after a laparoscopic examination of the biopsy. Transvaginal ultrasonography is usually paired with a physical examination; however, it is limited to more serious diagnoses and proximity locations. Diagnostic imaging (e.g., MRI) is beneficial, but it is expensive and sometimes overlooks the earliest stages of endometriosis, limiting its usage. The precision and dependability of biomarker use, particularly in the early stages of endometriosis, is lacking, particularly when it comes to serum markers like CA-125.[9]

Unfortunately, there is no standard treatment for endometriosis because the condition appears differently in everyone. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as the first line of therapy for endometriosis, followed by hormone therapy. NSAIDs are frequently used first since they are reasonably safe, readily accessible over the counter, and helpful for women with primary dysmenorrhea. Potential therapies for endometriosis include gonadotropin-releasing hormone (GnRH) agonists and antagonists. GnRH antagonists prevent the growth of endometriotic cells by suppressing the pituitary's synthesis of gonadotropin hormone and inducing a dose-dependent hypo-estrogenic condition.[10]

Following the failure or intolerance of conventional therapy, surgical management is used as a last resort. Laparoscopy, or conservative endometriosis treatment, is one of the primary surgical approaches. Furthermore, endometriosis, uterine prolapse, and uterine cancer are

among the many uterine disorders for which hysterectomy is a common treatment. Total uterine excision may result in additional difficulties, such as niching the incorrect uterine arteries, which could impede blood flow or cause a large amount of blood loss.[11]

Over the past few years, artificial intelligence (AI) has grown quickly, beginning to be used in a variety of disciplines, including healthcare. Machine learning (ML), a branch of artificial intelligence, enables computers to automatically identify patterns in huge, complicated datasets and utilize those patterns to forecast future events. AI is becoming more and more useful in the healthcare industry. Several machine-learning approaches have been applied to enhance the effectiveness of assisted reproductive technology (ART). AI has been utilized in the analysis of multi-omics, medical, behavioural/wellness, environmental, research, and developmental data. It has also been employed in drug discovery, decision-making processes, patient self-management, triage, and understanding disease causes. The integration of AI and reproductive medicine is certain to provide a crucial route for medical advancement, notwithstanding several obstacles.[12]

AI IN ENDOMETRIOSIS DIAGNOSIS

Over the past few years, research using AI techniques for the diagnosis of endometriosis has been widespread. AI was utilized for predicting the occurrence of endometriosis and building diagnostic models. Various Machine Learning methods were used to analyze large data to identify diagnostic signatures—most studies aimed to develop less invasive diagnostic methods.

MicroRNA (miRNA) was utilized in the ENDO-miRNA study to create a blood-based diagnostic signature for endometriosis because miRNA dysregulation is a critical component of the disease. The miRNA of 200 patients was analyzed using the Random Forest, Logistic Regression, eXtreme Gradient Boost, and AdaBoost techniques. This study revealed the first blood-based diagnostic biomarker. The results were more significant than the diagnostic surgery, with a sensitivity of 96.8% and a specificity of 100%.[13]

Using next-generation sequencing (NGS) and AI for the sequencing and analysis of miRNA, the multicenter prospective ENDOmiRNA Saliva Test study produced a 109-miRNA saliva signature for endometriosis. The discovery of a saliva-based miRNA signature offered up new avenues for the disease's early and noninvasive diagnosis.[14] Support vector machines were employed in a different study to examine 123 metabolites found in the Endometrial Fluid (EF) of endometriosis patients and controls. This study found that the lipidomic

composition in the EF was linked to ovarian endometriosis, indicating that EF analysis might be taken into consideration as a less intrusive method of endometriosis diagnosis.[15]

Some studies made use of protein spectra to build diagnostic and predictive models. A study comparing Raman spectra from 94 serum samples from 49 patients and 45 healthy individuals used Principal Component Analysis (PCA), k-nearest Neighbors (kNN), and Support Vector Machines. The results showed that the kNN-weighted model provided the best classification model with sensitivity and specificity values of 80.5% and 89.7%, respectively.[16]

Another study aimed to identify predictive biomarkers using partial least square discriminant analysis, multi-layer feed-forward artificial neural networks (ANNs) and quadratic discriminant analysis (QDA) modeling tools by analyzing serums of infertile women with endometriosis and control group. The QDA model was more efficient in predicting endometriosis, while ANNs provided criteria for diagnosis.[17] Five significant biomarkers of eutopic endometrium in endometriosis were found using artificial neural networks and protein fingerprinting with a sensitivity of 91.7% and specificity of 90%.[18]

The IMAGENDO system, developed by the Robinson Research Institute at the University of Adelaide, uses AI to analyze data from ultrasound and MRI to reduce the time it takes to diagnose endometriosis. The system combines MRI and ultrasound technology to provide fast, non-invasive endometriosis diagnosis, reducing the risk of anxiety, depression, and fatigue associated with the lengthy diagnostic journey.[19]

A questionnaire was developed to self-report endometriosis symptoms, based on 56 commonly found symptoms. The importance of these symptoms for endometriosis prediction was analyzed, and a subset of symptoms with the highest prediction accuracy was identified. A model was developed to predict endometriosis in the general population with 94% accuracy, which is to be integrated into a website for women to self-test and determine their endometriosis risk, recommending early diagnostic examinations.[20]

AI IN ENDOMETRIOSIS TREATMENT

The major concern for patients with endometriosis is infertility, AI has been improving the efficacy of ART. A questionnaire-based algorithm was created to identify women at risk for endometriosis, allowing for earlier treatment and better fertility outcomes. The algorithm can detect and report simple gamete production values as normal, abnormal, spontaneous, or

stimulated. This technology can greatly assist infertile couples during their diagnostic and treatment journeys. Clinical management is made more efficient by the gonadotropin starting dose calculators and the trigger timing upon controlled ovarian stimulation applications.[21]

Understanding endometriosis-associated infertility mechanisms and potential non-hormonal targets is crucial to improving fertility treatment, as current hormonal suppression methods may cause side effects. In cancer and several reproductive disorders like endometriosis and recurrent pregnancy loss, non-coding RNAs (ncRNAs) swiftly evolved into significant regulatory molecules. A study using a chimeric mouse model of endometriosis found that selective inhibition of prostaglandin receptors (EP2/EP4) can restore the interaction between prostaglandin E2, oestrogens, and progesterone in the eutopic endometrium of women with endometriosis, decreasing pro-inflammatory cytokine production and increasing P4 signaling.[22]

A study used differential gene analysis, WGCNA, and machine learning algorithms to explore senescence-related genes associated with endometriosis. The analysis identified a cluster of genes, including BAK1, LMNA, and FLT1, which could be used to develop potential immunotherapeutic regimens or pharmaceutical agents for clinical implementation.[23]

The study utilized three endometriosis datasets and a support vector machine model to identify biomarkers for endometriosis, with five genes (CXCL12, PDGFRL, AGTR1, PTGER3, and S1PR1) identified as biomarkers engaged in biological processes related to transmembrane transport and labyrinthine layer morphogenesis. Potential medications for endometriosis therapy included 7 that target CXCL12, 49 that target AGTR1, 16 that target PTGER3, and 21 that target S1PR1.[24]

Resection of visible lesions can treat endometriosis-related infertility and pelvic pain, with minimally invasive surgery offering lower complications like trauma, infection, and hospital stay. Robotic surgery offers similar perioperative outcomes as traditional laparoscopy but may benefit most in complicated stage III and IV endometriosis cases. Robotic technology could enhance endometriosis surgery by addressing challenges in identification, predicting complexity, and reducing operative time for complex cases due to the heterogeneity of lesions.[25]

Though data regarding robotics' superiority over traditional laparoscopy is limited, the advantages of robotics include lower learning curves, greater accessibility for both patients

and surgeons, and a host of other advantages like 3D vision, tremor filtration, image magnification, and an extra "hand." Furthermore, in obese patients, robotic assistance lowers the chance of laparoconversion.[26]

AI IN SYMPTOM TRACKING

Wearable devices provide objective data for longer periods, enabling the use of patient-reported outcome measures (PROMs) to provide insights into symptoms and therapies in endometriosis. Digital technologies have been used in clinical trials to monitor symptoms and evaluate medication efficacy. Electronic pain diaries and daily PROMs have been developed for longitudinal assessment of interventions, allowing for longitudinal evaluation of hormonal treatments in endometriosis.[27]

Studies have been conducted using the “Phendo” app, a free smartphone app that was part of a citizen science initiative. Individuals can track a wide range of symptoms, including those connected to common endometriosis comorbidities, with the Phendo app. These symptoms include pain (by reporting location, description, and intensity), gastrointestinal (GI), or urinary difficulties. Phenotypes based on symptoms, medication use, mood, and other factors were derived from user data in a cohort study. The researchers concluded that these phenotypes were highly aligned with expert classifications for the moderate and severe phenotypes when analyzing cluster purity.[28]

A retrospective study was conducted using the data from the app to examine any association between exercise and pain symptoms. The study recommended exercise for managing endometriosis pain.[29] A second related study discovered a moderate correlation between the daily self-reports of exercise made using the Phendo app and the self-reported step counts and minutes spent engaging in moderate-to-vigorous intensity exercise (MVE) (obtained using accelerometers worn on the body).[30]

CHALLENGES AND DATA INTEGRATION

While AI has undeniably demonstrated its considerable strengths, it is essential to recognize that it is not without its shortcomings and drawbacks. These issues span across various domains, ranging from technical to ethical, legal, and bioethical dimensions.

Symptom tracking using smartphone apps can lead to variability in reporting adherence and missing data compared to conventional studies. Factors like pain or fatigue severity can influence reporting patterns, introducing bias into symptom-tracking studies. Therefore,

investigating these patterns and considering them in analysis is crucial to ensure accurate results.

Data portability, one of the technical problems, is the ability to move data from one device and format to another while maintaining readability. The variety and variability of big data make it particularly difficult to aggregate and arrange them into a single, cohesive framework that can significantly improve our knowledge of gynecological problems and female reproductive health. The increasing fragmentation and heterogeneity of data sources and types in today's digital age pose a significant challenge to the traditional notions of ethical consent, data access, and data sharing. As new forms of information are constantly being produced and stored across a wide range of platforms and devices, it has become more difficult than ever for individuals, organizations, and regulatory bodies to navigate the complex landscape of data privacy and security.[31]

Additional risks associated with big data include data privacy, which is managing data in a way that reduces the likelihood of data theft or breaches and guarantees the security of sensitive information. The rapid advancement in technology presents new risks and challenges to safeguarding sensitive information from unauthorized access and misuse by cyber criminals.[32]

Particularly about gynecology, and in general about human reproductive health, patient health status information is especially delicate. Concerns about privacy may also arise for women during pregnancy. Nonetheless, some research has shown that patients have a high degree of acceptance for big data and computational/digital technology (such as mobile sensors), with pregnant women feeling at ease using these gadgets to provide their doctors with information.[33]

FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

Utilizing patient and clinician perspectives and technological advancements, patients can benefit from tools and data collection interfaces for improved health management, symptom tracking, and early diagnosis. The goal is to document symptom timelines and share this data with clinicians for early diagnosis and surgical triage. Algorithmic models can use past and present manifestations of endometriosis to infer new patients' likelihood of operative procedures. Integrating questionnaires at all care levels, particularly in tertiary care, can improve the accuracy and trustworthiness of prediction models.[34]

Data mining can result in statistically significant parameters, and gynecologists should assist in decision-making and interpretation of results. Involving practitioners in translational research could expedite the transition from bench to bedside, fill knowledge gaps, and harmonize discovery bioscience and clinical care.[31]

AI systems will be more reliable as they become more validated, allowing for personalized medicine based on patient history. AI's intelligent summation of medical information and simultaneous monitoring of millions of inputs will enable research for personalized medicine and play a significant role in preventative medicine.[35]

CONCLUSION

In conclusion, a promising new area for improving women's healthcare is the intersection between endometriosis and artificial intelligence (AI). Endometriosis, a complex and chronic condition that affects a large percentage of the female population, presents diagnostic and treatment barriers. The delay in diagnosis, which ranges from 4 to 11 years, highlights the need for novel techniques to improve early identification and patient outcomes. AI has considerable potential for accelerating endometriosis diagnosis, with multiple studies investigating less intrusive and more accurate diagnostic procedures. Additionally, AI algorithms improve early intervention and fertility results. The use of AI in symptom tracking, aided by wearable devices and smartphone apps, provides a valuable technique for monitoring patient-reported outcomes and evaluating therapy effectiveness. However, issues such as data variability, portability, and privacy must be addressed to ensure the dependability of these technological tools. Artificial intelligence (AI) has great potential to drive progress in the field of women's health, including personalized medicine and better patient care.

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