The International Endometriosis Evaluation Program (IEEP Study) – A Systematic Study for Physicians, Researchers and Patients

Das internationale Endometriose-Evaluations-Programm (IEEP-Studie) – eine systematische Studie für Kliniker, Forscher und Patientinnen

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- biomarker
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Abstract

Introduction: Endometriosis is a heterogeneous disease characterized by a range of different presentations. It is usually diagnosed when patients present with pain and/or infertility, but it has also been diagnosed in asymptomatic patients. Because of the different diagnostic approaches and diverse therapies, time to diagnosis can vary considerably and the definitive diagnosis may be delayed, with some cases not being diagnosed for several years. Endometriosis patients have many unmet needs. A systematic registration and follow-up of endometriosis patients could be useful to obtain an insight into the course of the disease. The validation of biomarkers could contribute to the development of diagnostic and predictive tests which could help select patients for surgical assessment earlier and offer better predictions about patients who might benefit from medical, surgical or other interventions. The aim is also to obtain a better understanding of the etiology, pathogenesis and progression of the disease.

Material and Methods: To do this, an online multicenter documentation system was introduced to facilitate the establishment of a prospective multicenter case-control study, the IEEP (International Endometriosis Evaluation Program) study. We report here on the first 696 patients with endometriosis included in the program between June 2013 and June 2015.

Results: A documentation system was created, and the structure and course of the study were mapped out with regard to data collection and the collection of biomaterials.

Conclusion: The documentation system permits the history and clinical data of patients with endometriosis to be recorded. The IEEP combines

Zusammenfassung

Einleitung: Das Erkrankungsbild der Endometriose ist sehr heterogen. Die Diagnosestellung erfolgt häufig im Zusammenhang mit Schmerzen und/oder Sterilität. Es können aber auch keine Beschwerden vorhanden sein. Dies führt dazu, dass die Zeit bis zur definitiven Diagnose aufgrund verschiedener Diagnostik- und Behandlungsansätze unterschiedlich lang sein kann und die Diagnose teilweise hierdurch verzögert wird. Die Validierung von Biomarkern könnte zur Entwicklung eines diagnostischen und prädiktiven Tests beitragen, um besser beurteilen zu können, ob und von welcher Therapie eine Patientin profitiert.

Material und Methoden: Um diese Fragestellungen zu beantworten, wurde multizentrisch ein onlinebasiertes Dokumentationssystem eingeführt, das zur Implementierung einer prospektiven multizentrischen Fall-Kontroll-Studie, der IEEP (International Endometriosis Evaluation Program)-Studie, beiträgt. Im Zeitraum von Juni 2013 bis Juni 2015 wurden die anamnestischen und klinischen Daten von 696 Patientinnen erfasst.

Ergebnisse: Durch die Implementierung konnten der Ablauf und die Strukturierung der Studie, insbesondere die Datenerhebung und die Biomaterialsammlung, etabliert werden.

Schlussfolgerung: In dem Dokumentationssystem ist es möglich, anamnestische und klinische Daten von Patientinnen mit Endometriose so zu dokumentieren, um sowohl in Kombination mit Biomaterialien wissenschaftliche Fragestellungen im Rahmen der IEEP-Studie zu beantworten, als auch Daten zu Zertifizierungszwecken zu erheben.

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this information with biomaterials and uses it for scientific studies. The recorded data can also be used to evaluate clinical quality control measures such as the certification parameters used by the EEL (European Endometriosis League) to assess certified endometriosis centers.

Introduction

A range of different clinical symptoms can signal the presence of endometriosis, some of which may overlap. In one group of women, the presence of endometriosis is associated with pain. In another group of women, endometriosis presents as infertility. In a further group of women, endometriosis is an incidental finding and the women experience no or few clinical symptoms. The heterogeneity of the symptoms may lead to a significant delay in diagnosing the disease [1].

Surgical removal of endometriosis and systemic drug treatment can reduce or even eliminate the pain experienced by some of the women with the disease [2]. Some studies have reported a positive impact on fertility rates [2]. However, the interplay of factors which result in some women finding relief in therapy while other women experience no alleviation are still not entirely understood.

Research into endometriosis is currently moving in completely different directions. While some investigations are focusing on diagnostic tests which could identify the disease in most affected women as early as possible, other studies are attempting to identify those women in whom no intervention should be performed, either because the intervention will not help or because the affected women do not require treatment.

Following the publication of the human genome in 2001, molecular analysis methods have evolved rapidly and contributed to the development of many therapies and diagnostic tests for other diseases. There have also been significant improvements in data processing, allowing data to be usefully deployed in studies collecting epidemiological data. However, these efforts have not yet progressed very far with regard to endometriosis.

We report here on the introduction of an online documentation system which will be the basis for the IEEP (International Endometriosis Evaluation Program) study, a program which aims to investigate relevant clinical and molecular issues in an international research concept and which will additionally collect data for certification purposes.

Material and Methods

In the period from June 2013 and June 2015, endometriosis was diagnosed and treated in a total of 696 patients attending one of the 5 participating hospitals and surgical outpatient facilities. The data of these patients was recorded in an online documentation system.

The clinical information of patients was obtained from their patient records. These records include information on the patient's history and medical treatment, including information on the surgical intervention, the histological findings, and any further treatment. All patients for whom the clinical data were complete were included in the analysis.

At the time of data collection patients were differentiated and classified into one of two groups. Patients categorized into the Prevalent Endometriosis group had already been diagnosed previously at operation; in these patients endometriosis had either recurred or was still present. Patients classified into the Incidental Endometriosis group had just been newly diagnosed with disease.

Database design

Documentation of the patients' history and clinical data was done using an Oracle-based database with an electronic case report form (eCRF). The database meets all the requirements of a clinical study system. Data collection is based on appointments with healthcare professionals; the database can document adverse events and serious adverse events and will permit audits to be carried out. The eCRF collects data on 23 variables at registration and data on at least 41 variables are collected when documenting the patient's medical history. In addition, at least 22 endometriosis-specific variables are recorded; if the patient undergoes surgery for endometriosis, data on a further 18 variables are recorded. This allows the type of endometriosis diagnosis to be differentiated very precisely, with the data showing whether the diagnosis was made clinically or surgically and whether the patient has superficial, deep infiltrating endometriosis, and/or adenomyosis. Information on 10 variables is collected at follow-up. Data monitoring is done using a professional query verification process and a source data verification process.

Documentation in an online database system for therapists and patients

The online documentation system for this multicenter study can be accessed with a standard browser. Users do not require installation of a separate program. Access to the documentation system is obtained and controlled by entering a username and a password. The access to various tools is controlled by internal use rights.

Certification of endometriosis centers

Since 2006 medical facilities have been certified by the German Stiftung Endometriose-Forschung (SEF), the European Endometriosis League and the Endometriose Vereinigung Deutschland e.V. with the long-term goal of improving the quality of medical treatment of, the research into, and the teaching on endometriosis [3]. Essential prerequisites for certification as an endometriosis center is diagnosing and treating endometriosis in accordance with the guideline, cooperating with self-help groups and – in particular – the documentation of (anonymized) patient-specific data and data from patient follow-ups [4]. The latter information is queried in an annual report which also includes information on whether patients with endometriosis are treated in hospital or on an outpatient basis and whether they receive conservative treatment or undergo surgery. The IEEP study network and the collected data are used to compile the annual report.

Table 1 Clinical variables which could play a role in the pathogenesis and prognosis of endometriosis or allow a prediction to be made with regard to the therapeutic efficacy of different therapies.

Patient characteristics		Prevalent group (n = 202)	Incidental group (n = 494)	Total (n = 696)
Age (years) at documentation		Mean = 34.4 SD = 7.9 n = 202	Mean = 34.3 SD = 7.9 n = 494	Mean = 34.3 SD = 7.9 n = 696
Age (years) at first diagnosis		Mean = 29.7 SD = 6.9 n = 202	Mean = 34.4 SD = 7.8 n = 494	Mean = 33.0 SD = 7.8 n = 696
Age at menarche (years)		Mean = 12.6 SD = 1.4 n = 191	Mean = 13.0 SD = 1.5 n = 463	Mean = 12.9 SD = 1.5 n = 654
	≤ 11	41 (21.5%)	73 (15.8%)	114 (17.4%)
	12	57 (29.8%)	89 (19.2%)	146 (22.3%)
	13	43 (22.5%)	135 (29.2%)	178 (27.2%)
	14	32 (16.8%)	100 (21.6%)	132 (20.2%)
	≥ 15	18 (9.4%)	66 (14.3%)	84 (12.8%)
Menstrual cycle length (days)		Mean = 29.2 SD = 7.0 n = 108	Mean = 28.1 SD = 5.8 n = 273	Mean = 28.3 SD = 6.1 n = 381
	≤ 27	38 (35.2%)	93 (34.1%)	131 (34.4%)
	28	31 (28.7%)	97 (35.5%)	128 (33.6%)
	≥ 29	39 (36.1%)	83 (30.4%)	122 (32.0%)
Duration of menstrual bleeding (days)		Mean = 5.8 SD = 2.1 n = 124	Mean = 5.5 SD = 2.0 n = 360	Mean = 5.6 SD = 2.0 n = 484
	≤ 4	24 (19.4%)	93 (25.8%)	117 (24.2%)
	5	37 (29.8%)	135 (37.5%)	172 (35.5%)
	≥ 6	63 (50.8%)	132 (36.7%)	195 (40.3%)
Pregnancies (number)	Total	202 (100%)	493 (100%)	695 (100%)
	0	110 (54.5%)	296 (60.0%)	406 (58.4%)
	1	43 (21.3%)	91 (18.5%)	134 (19.3%)
	2	31 (15.3%)	65 (13.2%)	96 (13.8%)
	≥ 3	18 (8.9%)	41 (8.3%)	59 (8.5%)
Live births (number)	Total	92 (100%)	197 (100%)	289 (100%)
	0	17 (18.5%)	48 (24.4%)	65 (22.5%)
	1	38 (41.3%)	73 (37.1%)	111 (38.4%)
	2	30 (32.6%)	60 (30.5%)	90 (31.1%)
	≥ 3	7 (7.6%)	16 (8.1%)	23 (8.0%)
Abortions (number)	Total	92 (100%)	197 (100%)	289 (100%)
	0	77 (83.7%)	158 (80.2%)	235 (81.3%)
	≥ 1	15 (16.3%)	39 (19.8%)	54 (18.7%)
Oral contraceptive intake (ever and currently)	Total	156 (100%)	242 (100%)	398 (100%)
	Yes	151 (96.8%)	228 (94.2%)	379 (95.2%)
	No	5 (3.2%)	14 (5.8%)	19 (4.8%)
Body mass index (kg/m^2)	Total	200 (100%)	482 (100%)	682 (100%)
	< 18.5	8 (4.0%)	19 (3.9%)	26 (4.0%)
	18.5 to < 25	120 (60.0%)	319 (66.2%)	425 (64.4%)
	25 to < 30	44 (22.0%)	88 (18.3%)	127 (19.4%)
	≥ 30	28 (14.0%)	56 (11.6%)	81 (12.3%)

Results

The data on patients' medical history recorded in the database are summarized in **Table 1**. Patients are differentiated according to whether they have incidental or prevalent endometriosis.

Different times to diagnosis

When the documentation system was set up, the time of diagnosis was discussed and it became clear that the circumstances that lead to a diagnosis of endometriosis differ widely. The patient may present with a clinical suspicion of endometriosis; she may already be suffering from endometriosis or have undergone a previous operation; or, endometriosis may be diagnosed as an incidental finding during surgery performed for reasons unconnected to endometriosis. This combination of different possibilities results in different diagnostic pathways (**Fig. 1**) which need to be taken into account when processing the data.

The symptoms which lead to a diagnosis of endometriosis can be very heterogeneous. Patients may present with pain or infertility or both. Other patients may experience no symptoms with the diagnosis of endometriosis made as an incidental finding at surgery. To take account of patients' individual needs and to ensure that, as far as possible, all patients with endometriosis are included in the IEEP study, it was necessary to form different study cohorts (**Fig. 2**) as this will subsequently allow individual predictions to be made.

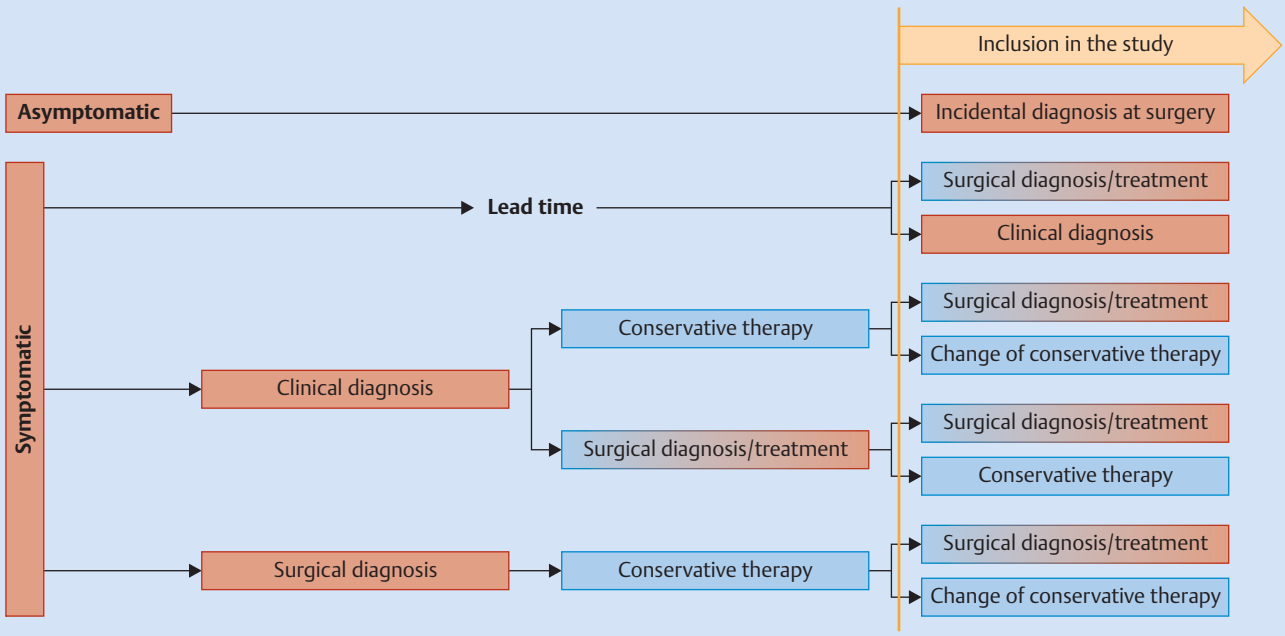

Fig. 1 Different scenarios until a diagnosis of endometriosis is made: in asymptomatic patients the diagnosis of endometriosis may be an incidental finding at surgery. But even symptomatic patients may be diagnosed with endometriosis in a number of different ways, through surgery or clinically.

Collection of biomaterials

The collection of biomaterials will play a central role in the IEEP study network. The collected biomaterials will be used to carry out high-quality patient-relevant analyses and will be combined with clinical information to validate a diagnostic and predictive test (**Fig. 3**). The aim is to find a predictive and diagnostic test which will predict the response to therapy as well as a predictive test which will predict the response to therapy over the course of disease after endometriosis has been diagnosed.

The procedure and process of collecting biomaterial was established with the introduction of the documentation system at the Gynecology Department of Erlangen University Hospital. Collection of biomaterials includes both material obtained at the first diagnosis of endometriosis and any biomaterials collected when

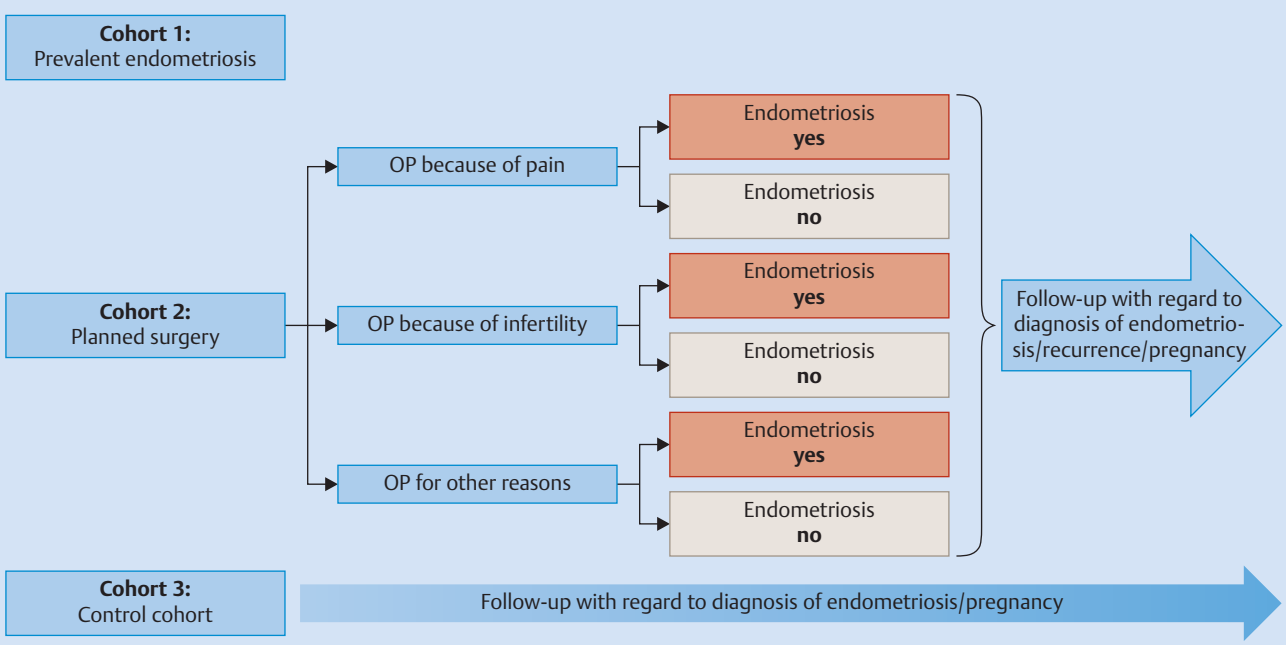

Fig. 2 Overview of the study cohorts of the IEEP study (OP: surgery).

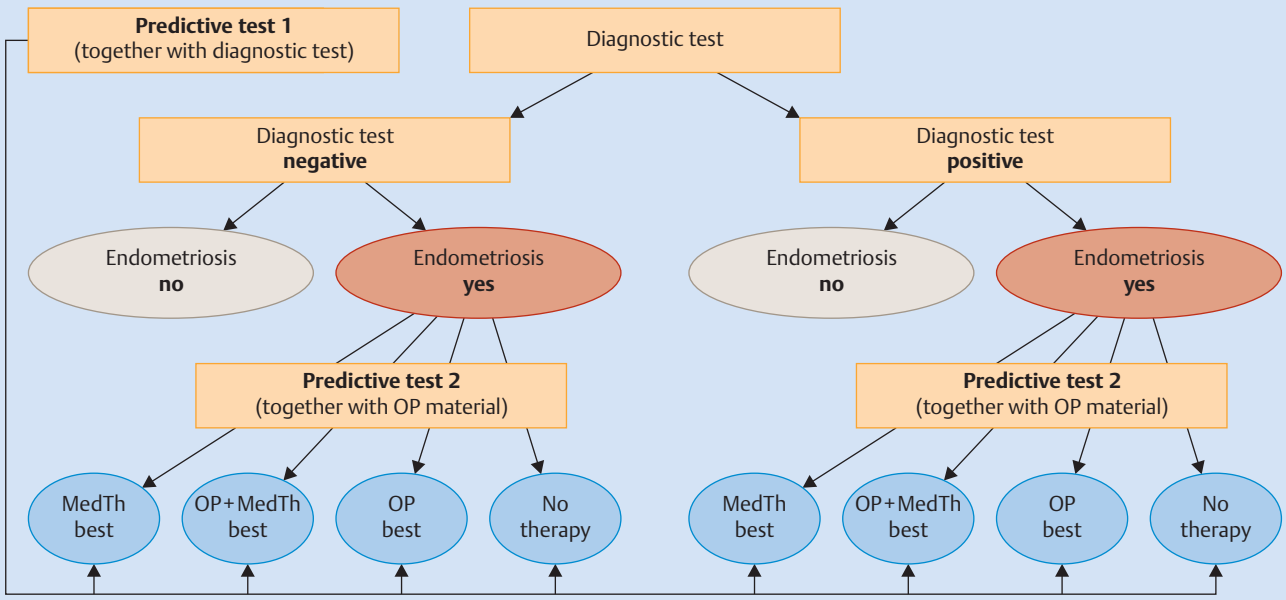

Fig. 3 Opportunities to implement a diagnostic or predictive test (OP: surgery, MedTh: drug therapy).

patients experience recurrence or a worsening of symptoms (**Fig. 4**).

Discussion

We report here on the introduction of an online documentation system for patients with endometriosis which is being used to establish the structures and processes of the prospective multicenter IEEP (International Endometriosis Evaluation Program) study. The aim is to validate a diagnostic and predictive test which will meet the different needs of patients.

The latency period between the first occurrence of endometriosis-specific symptoms and the diagnosis of endometriosis has been reported to be as much as 11 years [1]. A sensitive and specific non-invasive diagnostic test to diagnose endometriosis could lead to an earlier diagnosis of the disease. The advantage would be that no invasive diagnostics (i.e. surgery) would be required and the earlier time of diagnosis could prevent disease progression during the latency period. Although laparoscopy is generally considered to be a safe intervention with minimal risks and a low morbidity compared to laparotomy, complications can nevertheless occur, depending on the type of surgical intervention [5].

To validate a diagnostic and predictive test it is first necessary to identify patients who have been diagnosed with endometriosis. The most certain means of diagnosing endometriosis is by histological examination during surgical workup. But clinical examination and a review of the patient's medical history can also provide information which points to endometriosis. Depending on when the patient is diagnosed with endometriosis, this can lead to a number of different scenarios which data management must take into account.

In addition to a diagnostic test to diagnose endometriosis, a predictive test could offer help when making decisions such as whether surgical and/or drug therapy would be beneficial or whether the patient does not require therapy. A prospective observation of patients with endometriosis is necessary to validate any predictive test. For this it is important to create different study cohorts which will take account of the individual needs of patients.

Lower abdominal pain is one of the main symptoms of patients with endometriosis. Endometriosis is diagnosed in around one third of patients who undergo surgery for chronic lower abdominal pain [6]. As described in the guideline, a workup of characteristic symptoms must be done to establish or exclude a diagnosis of endometriosis, with the workup consisting of either laparoscopy or carefully calculated drug therapy [7]. With regard to disease progression, there are only limited data on the risks associated with repeat abdominal surgery or on increased pain in patients with endometriosis, as high or low pain levels have been found not to be correlated with the extent of disease [8]. There are also only a few studies on the efficacy of postoperative drug therapies (GnRH analogues, combined oral contraceptives or placebo) [9, 10]. In one study, only 6.6% of patients with deep infiltrating endometriosis and chronic pelvic pain who underwent surgery experienced recurrence, defined as a suspicious finding on rectovaginal examination, sigmoidoscopy or laparoscopy after 94 months [11].

The IEEP study aims to identify a cohort of patients and their clinical data and biomarkers, who were diagnosed with endometriosis after presenting with recurrent pain.

This cohort of patients with pain will be followed up prospectively with regard to the rate of recurrence, with recurrence defined as a worsening of symptoms or repeat abdominal surgery, and the impact of various therapies will be evaluated in order to make predictions regarding various therapies.

Endometriosis is diagnosed during laparoscopy in a quarter of patients with infertility [12]. The association between endometriosis and infertility remains unclear, although various etiologies have been proposed and discussed [13]. Anatomical changes of the adnexa are accepted to be a potential cause. Other etiologies

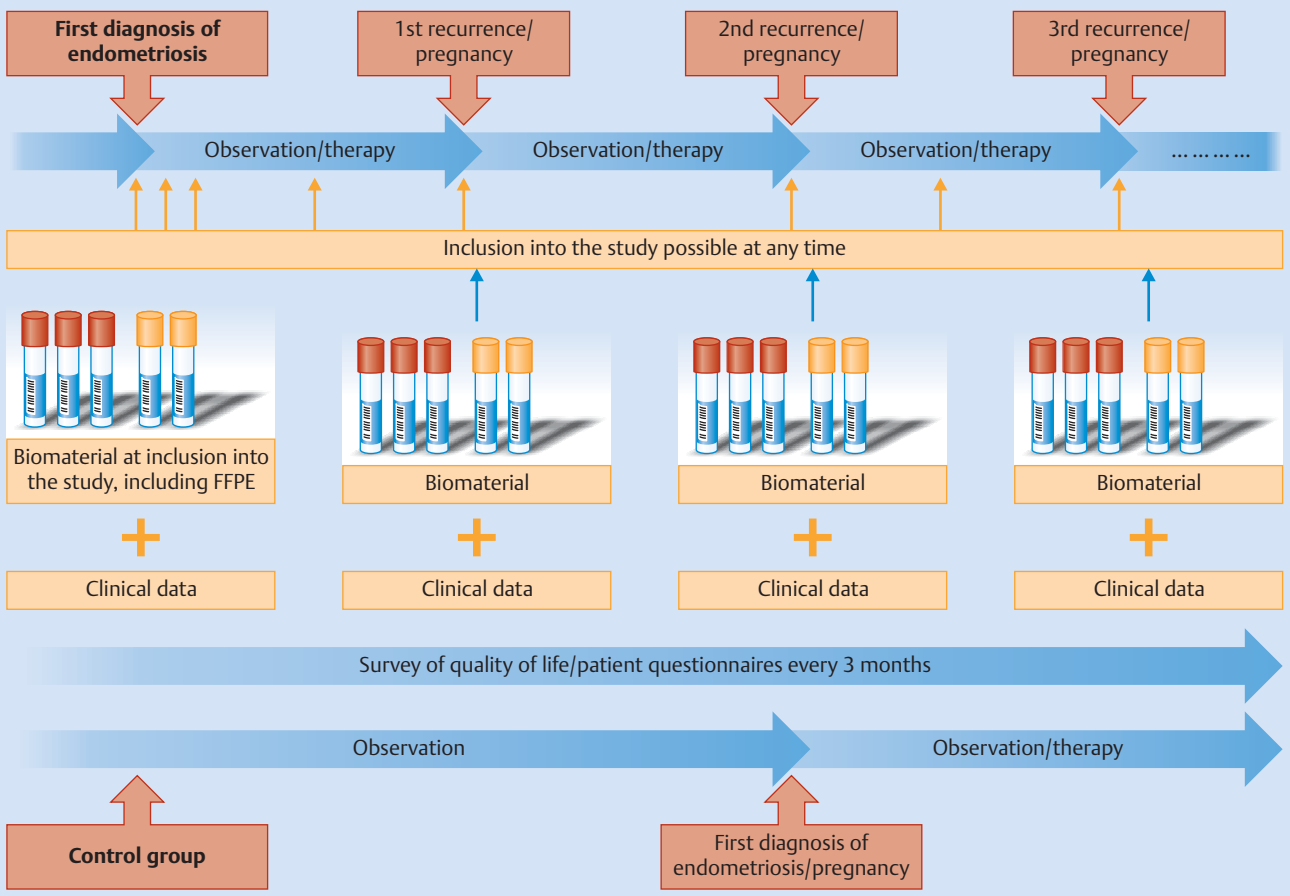

Fig. 4 Overview of the IEEP study: inclusion into the study for cases and controls at any time, thereby collection of biomaterial and clinical data and elevation of recurrence of endometriosis, pregnancies and optionally first diagnosis of endometriosis in the control group (FFPE: formalin-fixed, paraffin-embedded tissue).

include changes to the immunological milieu for implantation or affecting sperm motility, uterotubal transport disorders, and disorders of oocyte maturation [14, 15]. Published pregnancy rates for patients with endometriosis range from 24 to 54%, but these figures may be an overestimation as some patients did not attempt spontaneous pregnancy prior to surgery for endometriosis [16].

The IEEP study aims to contribute to validating a diagnostic and predictive test in patients with endometriosis and infertility, so as to be able to advise patients about the therapeutic approach and offer individualized therapy. Moreover, the study may result in a better understanding of the possible common etiology of endometriosis and infertility and allow the evaluation of pregnancy rates in a large patient population.

No correlation has been found between severity of symptoms and the extent of endometriotic lesions [17]. Endometriosis is diagnosed as an incidental finding in 5–25% of patients who undergo laparoscopic surgery for other reasons, such as tubal ligation [12, 18, 19]. In 2009, a multicenter study confirmed that the prevalence of adenomyosis is the same in women with uterine fibroids, endometriosis, pelvic pain or abnormal uterine bleeding and those who had none of the above-mentioned disorders [20]. In the IEEP study the cohort with incidental diagnosed endometriosis will serve as a comparative cohort to the two other cohorts of patients with pain and patients with infertility and contribute to the validation of a diagnostic and predictive test as well as finding an answer to the question whether these asymptomatic patients benefit from therapy or not.

It is important to ensure that the number of patients wrongly identified by the diagnostic test as negative for disease is as low as possible, as this will otherwise result in a continued delay in diagnosis and reduce the patients' quality of life. It is also important not to wrongly identify patients as positive for disease to avoid overtreatment and the wrong therapy.

The aim must therefore be to ensure the highest possible validity of a diagnostic or predictive test. This could be achieved by adding the patients' clinical data to the obtained biomarkers [21]. One of the most important advantages of validated biomarkers will be that they can be used to diagnose endometriosis and monitor disease quickly, cost-effectively and non-invasively. Possible biomarkers include peripheral biomarkers in blood, such as growth factors, hormones, proteolytic enzymes, glycoproteins, soluble adhesion molecules, immunological cell changes, autoantibodies, miRNA, circulating cell-free DNA, and cytokines [22], and tissue obtained during surgery.

In the context of the IEEP study, biomarkers and clinical data will be collected and recorded on inclusion into the study and at every recurrence or worsening of symptoms.

The goal of this collaboration between centers is to process the information obtained in such a way that differences in the treat-

ment provided by the participating centers are made visible, prompting a debate about these differences. Patients can contribute to the evaluation by completing specific questionnaires and the information obtained can be shared with the patients. In the current age of information, data collection and documentation should not only be used to collect data for studies but also deliver a direct and immediate benefit for the patients, as well as for the participating centers.

Conclusion

There is little information available which could help predict the course of endometriotic disease or the course of therapy and the response to different therapies. Treatment center networks, research networks and study networks need to focus and combine their resources to ensure that patients receive the best treatment available and need to cooperate to develop individualized treatment concepts. Working in the interest of patients with endometriosis, these are the goals the IEEP study network has set itself.

Conflict of Interest

The authors declare no conflicts of interest.

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