Shared decision-making in the context of evidence-based medicine

Case study: an approach to reparative reproductive medicine

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There are no uninteresting things,
only uninterested people.
- Gilbert K. Chesterton

Declaration

I declare that this document is an original work of my own authorship and that it fulfills all the requirements of the Code of Conduct and Good Practices of the Universidade de Lisboa.

Preface

The work presented in this thesis was performed at the Centre for Management Studies of Instituto Superior Técnico, Lisbon, Portugal, during the period January-October 2019, under the supervision of Prof. Mónica Duarte Correia de Oliveira.

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To all professors and colleagues I met and worked with throughout these five years. Thank you Sara for being my right hand. For all the presentations, group works and projects, late nights and stress times. All that brought me to where I am today, and for that I am grateful.

To my parents, brothers and sisters, for their support over it all. Thank you for somehow inspiring me for the theme of this dissertation.

This dissertation could not have been done only by me, so thank you all.

Abstract

The healthcare industry is trying to reinvent itself in a time where patient engagement is the challenge. Enormous amounts of information available, and conflicting advice from clinicians, media sources, acquaintances may arise, making the decision-making process difficult. Concepts like Evidence-based medicine, or Shared decision making, define approaches and frameworks on how to exercise health care. In the past few decades, contraception, abortion, sterilization and artificial reproductive technologies are the primary fields of research and in the literature of reparative and reproductive medicine. Therefore, research towards classifying the underlying causes of gynaecological conditions and infertility has been neglected.

This dissertation will assess Shared decision-making in the context of Evidence-based medicine in reparative reproductive medicine. Fertility*Care* will be compared to the concept of Evidence-based medicine. Following that, the 9-item shared decision-making questionnaire will be administrated to all women and couples enrolled in the project. This will be performed to appraise the Participants perception of SDM.

The average SDM-Q-9 transformed score was of $83,3$. Results were then analysed considering the consultation purpose. General follow-up to revise the charting method, Family planning consultation either to avoid or achieve a pregnancy, appointments to assess the couples' Infertility, Post-partum follow-up, and pregnancy were the five groups considered. Based on the consultation purpose of the participants, different perceptions regarding SDM lead to different overall scores on the SDM-Q-9 survey.

SDM-Q-9 is subjective and presents several limitations. It cannot truly capture the absolute level of SDM but it indicates that Fertility*Care* is perceived as such by its participants.

Keywords: evidence-based medicine, shared decision-making, patient engagement, fertility awareness-based method

Resumo

A prestação de cuidados de saúde precisa de se reinventar, quando o presente desafio é obter maior envolvimento dos pacientes. A vasta informação disponível, conselhos dos profissionais de saúde, os media, e opinião de conhecidos torna a tomada de decisão difícil. Novos conceitos como a Medicina baseada na evidência, ou a Decisão clínica partilhada, definem novas abordagens e modelos para práticas clínicas. Nas últimas décadas, contraceção, aborto, esterilização e reprodução medicamente assistida são as principais áreas de investigação e as mais presentes na literatura no que toca à medicina reparativa e reprodutiva. Portanto, há negligência na investigação em torno das causas de doenças ginecológicas e infertilidade.

Esta dissertação procura avaliar o processo de decisão clínica partilhada no contexto de medicina baseada na evidência na área da medicina reparativa e reprodutiva. O projeto Fertility*Care* é comparado com o conceito de medicina baseada na evidência. De seguida o 9-item shared decision making questionnaire vai ser feito às mulheres e casais que participaram no projeto, para avaliar a perceção de decisão partilhada.

A média geral da pontuação do SDM-Q-9 foi de $83,3$. Os resultados foram depois analisados segundo o propósito da consulta. Consulta de seguimento, consulta de planeamento familiar, consulta de seguimento pós-parto, consulta de infertilidade e acompanhamento de gravidez foram os cinco grupos analisados. Baseado no contexto da consulta, diferentes perceções de DCP justificam diferentes pontuações no SDM-Q-9.

O SDM-Q-9 é subjetivo e apresenta limitações. Não consegue efetivamente capturar o nível de DCP mas indica que o Fertility*Care* é percecionado como tal.

Palavras-chave: medicina baseada na evidência, decisão clínica partilhada, envolvimento do paciente, métodos de controlo de fertilidade

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Glossary

ART - Assisted reproductive technology.

BBT - Basal body temperature.

CrM - Creighton model.

EBM - Evidence-based medicine.

FABM - Fertility awareness-based method.

FSH - Follicle stimulating hormone.

GnRH - Gonadotropin releasing hormone.

hCG - Human chorionic gonadotropin.

ICSI - Intracytoplasmatic sperm injection.

IUI - Intrauterine insemination.

IVF - *in vitro* fertilization.

LH - Luteinizing hormone.

NaProTECHNOLOGY - Natural Procreative Technology.

RS - Raw score of SDM-Q-9.

SDM - Shared decision-making.

SDM-Q-9 - 9-item shared decision-making questionnaire.

TS - Transformed score of SDM-Q-9.

Chapter 1

Introduction

In an era of information, modern society tries to make the most of the resources they have. More even in healthcare related matters. Health industry is trying to reinvent itself in a time where the patient is the center. For that, recent concepts like Evidence-based medicine (EBM), or Shared decision making (SDM), try to define approaches and frameworks on how to exercise health care.

Over the last few decades, contraception, abortion, sterilization and artificial reproductive technologies (ART) are the primary fields of research and in the literature of reparative and reproductive medicine. Hence, scientific evidence and research towards classifying the underlying causes of gynecological conditions and infertility has been somehow neglected.

The present dissertation will assess SDM in the context of EBM in reparative reproductive medicine.

1.1 Motivation

In present society, individuals are becoming more engaged with their own healthcare. Enormous amounts of information are all around us, and there is a high offer of healthcare services and resources available [1]. Given this, conflicting advice from health professionals, media sources, friends and family arise, and the decision making process on how to proceed becomes difficult.

The best way to engage patients in healthcare is a hot topic of discussion. Terms like EBM and Patient-centered care or SDM appear as experimental terms to describe the best way to deliver healthcare. Large is the amount of literature published on these topics, but concrete cases of their application are scarce.

The topic of Family planning and infertility is not clearly discussed. The answers to the first go to the use of artificial contraceptives and the solution to the later is recurring to ART's [2]. No foundations on women's health are at the focus of sexual education, and no attention to the causes of infertility and possible treatment solutions are targeted, just the solution.

Fertility awareness-based methods (FABM) appear as important tools to both women, couples and healthcare professionals. Whether through apps, calendars, or small gadgets, these are used not only to identify fertile and infertile periods, but as an indicator for women's health.

The Creighton Model (CrM) Fertility*Care* system is based on the standardized observation and chart-

ing of biomarkers to assess a women's health and fertility. Its areas of intervention are infertility, spontaneous recurring miscarriage, family planning and woman's health [3].

With this dissertation, the objective is to explore this recent reparative and reproductive medicine project in Portugal as an approach to the practice of SDM.

1.2 Topic Overview

Patient engagement in healthcare challenge is the main topic at hand. It is present in the concept of EBM, defined as the conscious, explicit and judicious use of the current best evidence [4] in the relation between a clinician and patient with the purpose of resolving, or coping with physical, mental and social problems related with the patient's health [5], considering the patient's values, preferences and expectations.

Shared decision-making can be considered as a specific application of the best available evidence, clinical expertise and patient preferences and applications. This approach appears as a process to contrast with the usual way to provide healthcare. By making both the patient and healthcare professional with active roles in the decision-making process, and enrich it with the individuals own expectations and preferences.

Women or couples can use the CrM Fertility*Care* system as a family planning approach to evaluate the natural fertile and infertile periods of the cycle. And, through the charting of biological markers it is possible to discover and track abnormalities in a woman's health. To this purpose, there is a standard teaching set-up and language to classify the biological markers provided by an accredited practitioner or medical advisor. Furthermore, the model is supported by a thorough ongoing research, accredited teaching programs for the healthcare professionals and standard teaching format throughout its centres of practice [3].

1.3 Objectives

The main objective of this dissertation is to potentially demonstrate Fertility*Care* as a SDM approach, evidence-based. With that purpose, a qualitative appreciation of the CrM Fertility*Care* system being evidence-based will be performed. And to evaluate it as a SDM approach, the 9-item shared decision-making questionnaire (SDM-Q-9) was administered to the participants.

There is also a purpose to present this project as a FABM to consider as a complimentary and auxiliary tool for women and couples that experience infertility, spontaneous recurring miscarriage, or intend to find a family planning approach not based on artificial contraception or are even just checking their own health. So, the main objectives for this work are:

- Understand the concepts of EBM and SDM, to comprehend the theory on the best approaches for patient engagement;
- Analyse the state of the art of FABM's;
- Identify the existing approaches to get around Infertility;

- Describe the CrM Fertility*Care* system;
- Evaluate Fertility*Care* as a SDM approach;
- Analyze and discuss the results.

1.4 Thesis outline

The dissertation will begin with the definition of the problem, where some important concepts will provide context to the work to be developed.

In the literature review, the *state of the art* of what refers to EBM, SDM is presented. Scientific evidence on the menstrual cycle and women's health and infertility are also items in review in this chapter.

The Fertility*Care* case study is then presented, followed by the data research and methods to be applied. Namely the SDM-Q-9 and the statistical tests to analyse the results.

Finally, the results are presented and analysed, conclusions can be retrieved and future work considered.

Chapter 2

Definition of the problem

This chapter was set to present the problem at hand in this dissertation. Patient engagement in healthcare as a challenge in current healthcare practice was presented as the main topic in discussion. SDM is then presented as an approach to consider the patient as an equal part in the decision making process.

The specific clinical area of reparative and reproductive medicine is then presented as the focus for the research of this work. Woman's health and Infertility are the matters under considerations, together with FABM's.

The chapter that follows will explore the concepts more in depth, to construct a theoretical basis for the study.

2.1 Patient engagement in medical care

Patient engagement in their own health care has become a reality in the last few decades. The search for healthcare services is turning into a complicated process given the enormous amount of data and resources available. Conflicting advice is a concern when an individual hears different insights from clinicians, friends and family, and even the advances in media and information technologies means [6].

Nowadays, people are at freedom whether or not to seek care and want to manage their health status. They also expect timely, reliable and effective care, where the health providers should meet their needs to give adequate information and support and demonstrate empathy and respect for their condition. However, an effective engagement implies the collaboration and support of the healthcare professional to the individual patient. Clinicians are only responsible for half of the effort to help their patients to achieve the best possible state of health [7]. Some aspects may be good indicators of patient engagement in healthcare [8]:

- Quality of doctor-patient communication;
- Access to different sources of information and advice;
- Preventing care and advice provision;
- Informed choice of medical care provider;

- Risk communication and involvement in decisions on treatments;
- Self-care and self-management support.

Challenges arise when the medical literacy is poorly understood by the person or there is a lack in skills and motivation on the professional side. The necessity to enable greater patient embroilment in medical care can begin by making the best evidence on the most effective strategies more accessible for always busy healthcare practitioners.

2.1.1 Improving medical literacy

Many are the approaches to improve the individual's ability to understand medical literacy and act upon it. Formal health education and directive styles of giving advice have been overridden by newer programs and ideas.

Motivational interviewing for example, ought to encourage patients to adopt more healthy behaviours instead of just pursuing what the doctor instructs. Targeted interventions with provisioning of written and electronic information. e-learning programs and virtual support empower the individual with accessible health information material. The more personalized information the person gets, the greater impact in their engagement [8].

2.1.2 Shared decision-making and patient engagement

SDM, can be described as the process by which a decision that regards a patient's health should be made by information exchange and deliberation between the healthcare professional and patient, followed by a consensual decision [9].

SDM implies evidence-based information on the condition, treatment options, benefits and risks. Together with the support and guidance of the clinician and the registration and consideration of the patients preferences and concerns.

Health coaching and personalized care planning can help, for instance, individuals with long-term conditions so they can more easily manage their own health status. Self-management courses and support for chronic-condition patients is also a method to develop patient knowledge and engagement.

Decision aids

From simple fliers with information, to computer programs, Decision aids have been developed to support the decision making process.

Information addressing various topics on prevention, diagnosis and treatment procedures can guide the individual in decision making. Furthermore, Decision aids can be used in structured counseling by health professionals.

These methods can lead to increased patient participation, more knowledge on options' outcomes and risks, and greater confidence with decisions. However, not all available aid tools respect the standards of being evidence-based and complete, unbiased and intelligible for the person [10].

2.1.3 Quality of care processes

Processes can be evaluated and improved based on the feedback given by patients. Either by gathering individual responses from surveys, or by feedback meetings, there is now a wide data base for what patients identify as important and good health care. Performance data from health centers is now available to the public. This impacts the healthcare providers since it is a stimuli for continuous quality improvement [8].

Feedback from clinical care outcomes reported by patients also impacts diagnosis and condition management approaches as it raises the clinicians awareness. Physicians and health professionals often experience barriers to a more evidence-based practice. Gathering their experience with the best quality medical literature and consider the patients preference and personal case is a great challenge in an environment where time lacks [11]. Development of communication skills is a requirement for optimal patient care. The ability to clearly explain the conditions, treatment outcomes on benefits ans risks and supporting the patient understanding. The main strategies to overcome knowledge, attitude and practice limitations are education and training.

2.2 Fertility awareness

In our present society, there is a trend to postpone childbearing within the reproductive-age population. The decision might not be fully conscious, as besides the individual reasons, there are numerous others such as social and economic factors or existing policies. This trend appears to be related with an increase in the incidence of infertility [12].

Infertility is a public health problem, and can be associated with health conditions or risk behaviours. Sexual transmitted diseases, smoking and other substances consumption, obesity or low weight among others. All this raises the necessity to develop and improve fertility awareness in the general population.

2.2.1 Infertility causes

Causes of infertility may dwell in a combination of female and male factors. Figure 2.1 presents the average of the etiology of infertility. The main female factors are ovarian dysfunction and tubal factors, that correspond to approximately 35% of all cases. Infertility caused by male factors cover 24% of the diagnostics.

The absence of ovulation or hormone function abnormalities are some of the causes that are at influence ovarian dysfunction. Anatomical abnormalities in the Fallopian tubes or endometriosis are among the tubal factors. Regarding male factors, ejaculatory dysfunction or infection conditions are some of the causes of infertility. Others can be undefined - idiopathic infertility - these constitute about 28% of the cases [13].

2.2.2 Looking for the right diagnosis

Infertility testing can be an expensive pursuit, sometimes involving invasive and uncomfortable procedures. Before starting the medical examinations and tests, the clinical history of the couple is investigated.

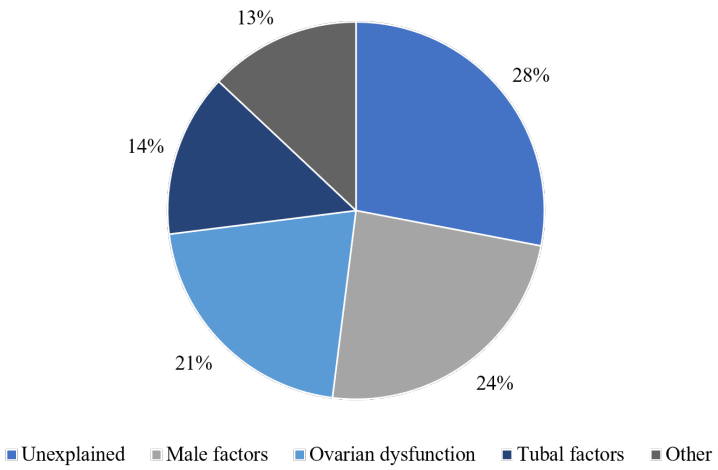

Figure 2.1: Etiology of infertility [13].

Their sexual habits and health-related behaviours are also assessed. From that, recommendations follow to improve or create new habits that can lead to a better change of achieving a pregnancy.

Infertility evaluation is performed on both men and women. Since fertility in men requires the testicles to produce sperm to be ejaculated into the vagina to meet the oocyte, and female fertility relies on the ovaries to mature and release oocytes for fertility, tests for infertility aim to find out if any of these processes are flawed [14].

Specific examinations for men include semen analysis, hormone assessment, testicular biopsy and others. For women, ovulation testing if the first test and hormone assessment follows. Contrast imaging to evaluate the anatomy and condition of the uterus and Fallopian tubes can also be done and in some cases, hysteroscopy can be performed.

Despite all the efforts to find a diagnostic, at the end it may be that no specific cause was found.

2.2.3 Fertility awareness methods

Fertility awareness from a woman or couples perspective can be an important tool for health professionals. Taking the female side as example, fertility awareness can be indeed an indicator to assess women's health, besides the usefulness to identify fertile and infertile periods [15].

FABM's help women and couples to identify the most fertile days and the infertile periods of the menstrual cycle in order to achieve or avoid pregnancy. They are defined as any method that used specific rules to assess approximately the fertile window based on the tracking of one or more of the following biomarkers: menstrual cycle duration, basal body temperature (BBT), cervical mucus, urinary hormones [16]. An overview of the most commonly used FABMs are:

- Calendar methods - consider the length of the cycle, where the fertile period is calculated based on prior cycles' duration.

- Mucus-only methods - based on the observations of the cervical mucus externally at vulva, the mucus consistency pattern determines the fertile window.

- Basal body temperature plus - considers the BBT and cycle length.
- Symptothermal single check - Cervical mucus and BBT assessment.
- Symptothermal double-check - Cervical mucus, BBT, cycle length and cervical position assessment.
- Hormone monitoring through urine - based on the hormones present in urine and the cycle length.
- Symptohormonal - based on the hormones present in urine and the cycle length and the cervical mucus.

2.3 Summary

Quality of doctor-patient communication, access to different sources of information, advice provision, encouragement for informed choices, risk communication as self-care support are good indicators of patient engagement in healthcare [8].

SDM arises as the process by which a consensus decision by patient and doctor is reached, based on information exchanged on both sides, options' appreciation and discussion and preferences and expectations considered. Information can be shared through Decision aids.

FABM's can be considered Decision aids. Through monitoring of biomarkers, information on the most fertile days and infertile periods of the menstrual cycle can be recorded and monitored so women and couples are made aware and can act upon it.

Chapter 3

Literature background

With this chapter, the concepts around EBM and SDM were described. Evidence needs to be of quality and accurate, to provide confidence in estimates and recommendations from clinicians. Models and fundamentals of EBM are presented as descriptions on the best theoretical approaches to exercise healthcare.

Trying to achieve a more specific concept, SDM appears as a direct application of EBM. Information, support, discussion and follow-through are the core elements of this practice and always need to be taken into consideration. Decision aids are evidence-based tools that provide help to patients, and support clinician's counseling in the decision making process. Many are the formats in which these tools are displayed.

To provide a clinical context to the case study of this dissertation, the scientific evidence on the menstrual cycle phases and endocrinology are described. Biomarkers of the menstrual cycle are defined and explained as observable and data that can be recorded and further analyzed.

The *state of the art* of women's health and infertility are discussed at the end of the chapter. Causes, diagnosis and treatment of infertility are explored as an admonition to the next subject where the Fertility*Care* case study is presented.

3.1 Evidence-based medicine

3.1.1 Definition

EBM has been a topic of use and discussion in healthcare practice, between clinicians, public health practitioners, purchasers, planners and the population in general, for over a century. Is defined as the conscious, explicit and judicious use of the current best evidence [4] in work between a clinician and patient with the purpose of resolving, or coping with physical, mental and social problems related with the patient's health [5], considering the patient's values, preferences and expectations.

3.1.2 The fundamental steps of Evidence-based medicine

EBM has at its foundation the integration of first the best quality published evidence, second the individual clinical expertise and judgment and third the patient's values and preferences [17].

Best available evidence

Rational clinical decisions are to be made using the best available evidence. Evidence concerning diagnosis, prognosis, and treatment, interpretations of test results and the impact of alternative strategies on patients' likely outcomes. Nowadays there is an enormous amount of medical literature, and healthcare professionals often lack time to follow the state-of-art of current evidence on specific research questions. Clinicians' own preconceptions, and unrepresentative and low-quality evidence are also situations to be considered when using evidence in decision making. Keeping track of published articles to critically appraise useful evidence can be achieved by recurring to systematic reviews, meta-analysis and clinical practice guidelines.[18]

A systematic review is by definition a summary of the medical literature regarding a specific question. The synthesis of multiple primary studies follows explicit and reproducible methods, in a way that respects a strict scientific design. Clinical tests regarding diagnostic, screening and prognosis, public health interventions, side effects, economic assessments and intervention studies are some of the areas that perform systematic reviews. These overviews construct justifiable conclusions about the effects of interventions. They also may indicate areas where medical and scientific knowledge lacks, giving leave for further research.[18]

Meta-analysis is a combination of analysis of independent primary studies regarding the same question. Results are gathered and evaluated using explicit statistical methods to produce a summary conclusion. Efficiency, generalizability, consistency, precision, and quantification of data are advantages of performing the meta-analysis. [18]

Systematic reviews and meta-analysis are on the basis of the clinical practice guidelines. The latter is developed to aid clinician and patient decide on the most appropriate health care given specific circumstances. After the systematic appraisal of the best evidence considering a particular clinical question, a consensus among healthcare professionals is necessary. A clinician's own personal experience is put together with other colleagues' professional expertise, creating greater agreement on the best opinion of a specific healthcare intervention. [19]

There are many sources of medical literature.[20] Meta-analysis, systematic reviews and clinical practice guidelines are types of information that passed through a process of selection, assessment of validity and importance analysis. They are considered filtered information since they synthesize and apply evidence like independent primary studies. Types of unfiltered medical information or raw evidence that are relevant for further appraisal, synthesis, and applications are as follows:

- Randomized control trials (RCTs) - A clinical trial that evaluates a specific outcome in one or more interventions in comparison to a control group. The participants are randomly assigned to each group. RCTs address interventions such as drug therapy, medical device or procedures.[20]

- Cohort studies - Observational study where investigators follow a group of people (cohort) undergoing a certain kind of treatment over a long period of time. It evaluates people habits and experiences with the purpose of finding out more about risk factors. They can be expensive and time consuming.

- Case-control studies - Observational study where investigators follow two groups, one who has a disease and other as a control group. The purpose is to look back at the person's history and find out whether it may have occurred exposure to a given risk factor. They are not quite expensive nor time-consuming, but they can be less reliable.[21]

- Case reports or case series - Studies that contain the description of a single patient of a group of patients on a particular aspect of the disease or condition.

- Background information and expert opinion

Confidence in estimates

When in the exercise of EBM, one needs to go for the best evidence possible. One question then arises. "What is the best evidence?" Hierarchies of Evidence and frameworks for judging confidence in estimates exist to provide a level of confidence to the different types of studies presented earlier. To exercise rational clinical decision making one needs to weigh the advantages and disadvantages of alternative strategies and estimates. The different estimates will have different levels of confidence.

The traditional pyramid of evidence is represented in several ways. Either considering the risk of bias or the applicability or even both it is used to describe the sources of evidence to be used in EBM. Systems of evidence, like reviews and meta-analysis, are a result of the integration of information from the lower levels [22]. Together with individual patient records that are present in clinical practice guidelines, they represent the top of the pyramid. The lower levels comprise single studies. From weaker to a stronger position, clinical evidence is ranked according to the strength of their freedom from various biases. In Fig. 3.1, one perceives the relative importance of the different sources of evidence, excluding the systems of evidence. Clinical experience and expertise are indeed helpful for the process of decision making, but they appear at the bottom layer.[23]

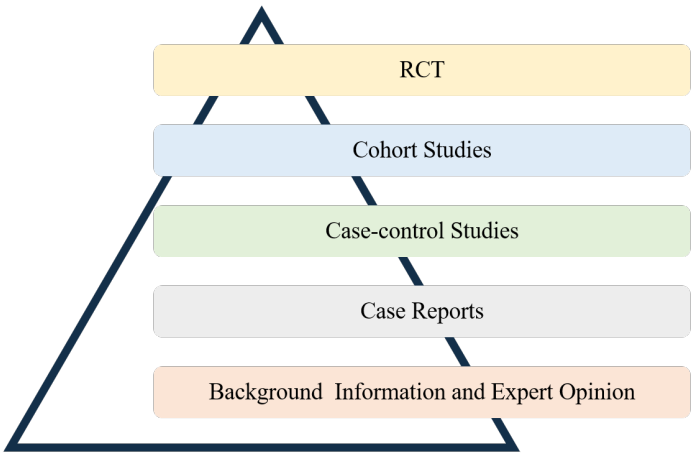

Figure 3.1: Pyramid for the Hierarchy of Evidence.

The framework created by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) judges confidence in estimates of effects of healthcare interventions. It provides a way

to categorize quality of evidence and strength of recommendations.[24]

Confidence in the quality of evidence may decrease for various reasons. Study limitations, inconsistency, and imprecision of results are some of the factors that can do so. Classification of evidence is in one of four levels. From high to moderate, low and very low. For high-quality evidence, one assumes that further research would not change the level of confidence in the estimate. There is confidence that the effect of the intervention will be close to that of the estimate. In moderate-quality evidence, the possibility that the effect of the intervention can be substantially different from the estimate implies the need for more research to increase confidence. In the two lower levels of quality, more research is indeed necessary to impact on the level of confidence in the estimate. Uncertainty in the estimate of effect is a boundary to resolve in very low-quality evidence.

The strength of a recommendation is influenced by several factors. The most obvious is the quality of evidence. Uncertainty in the balance between desirable and undesirable effects or in the wise use of resources for a given intervention and variability in values and preferences are other circumstances. The GRADE framework proposes two grades to evaluate a recommendation. A strong recommendation is when the trade-off between benefits and downsides of an intervention favor a desirable effect. Contrarily, when there is uncertainty in the trade-off, one provides a weak recommendation. When desirable and undesirable effects are evenly balanced, or the quality of evidence is considered low, it will be a weak recommendation.

Patient's values and expectations

Consider patient unique values and preferences is the final step in the practice of EBM. And the most difficult to implement. EBM is about the integration of the patient values with the best available clinical evidence. It is a fact that no matter how high the quality of evidence we have or how accurate the estimates on effects appear there is always the imperfect and limited ability of the clinician and the variability among the individual patient values.[25] Rational clinical decisions need to be consistent with personal hopes, goals, expectations, predispositions, beliefs, politics and religion.[5]

Some key elements have a critical influence on EBM.[25] Values have a strong influence in decisions regarding which are the technologies and interventions to be developed in early scientific research. The method to perform for example RCTs is controlled and oriented to provide unconfounded results in an atypical scenario. The specific circumstances where the studies are performed lead to findings and conclusions off from a real-life situation. To extrapolate conclusions to apply in EBM one needs the judgment from experience of healthcare professionals and the patient's background. There is a need to bring out the patient's values and find a way to combine them into clinical decision-making.

The 5 step model

EBM aims to improve the quality of care by identifying and advancing with best practices and eliminating and discontinuing ineffective and harmful interventions.[17] The effectiveness of clinical interventions, the accuracy, and precision of diagnosis and prognosis are demands of the critical thinking promoted by EBM. Therefore, it is important for healthcare professionals to develop skills to find, critically appraise

and incorporate evidence as well as to take into consideration the patient's values to make the best clinical decision. EBM involves 5 steps.

STEP 1: Formulating clinical questions

A well-formulated clinical question formulated from a clinical problem is at the basis of EBM practice. The answer to the question should be possible through the research in medical literature. It is an agreed subject through researchers that an answerable clinical question should follow a PICO (Patient/Problem, Intervention, Comparison, Outcomes) structure.[17] Patient or the population that is of interest to the clinical problem. Which is the intervention to evaluate? One needs to describe it thoroughly. Comparison or control are the main alternatives compared with the intervention that will be analyzed. And finally what is the most important outcome of the intervention for the patient?

STEP 2: Finding the evidence

From the first and second fundamental steps of EBM, one has present the aspects to consider when seeking relevant evidence to answer clinical questions. For different kinds of questions, there are different types of evidence to consider. There are several sources of evidence, such as textbooks and journals. Many of these available now on the internet. Along with online electronic bibliographic databases, where thousands of articles are available to research. Given the amount of information at disposal, and the scarce time to retrieve the most relevant articles, there is a need to be effective. In this way, healthcare professionals need to have or have training in search skills. Using appropriate keywords to conduct the research given the clinical question to use in a bibliographic database.

STEP 3: Appraising the evidence

It was discussed that there is a need to assess the evidence validity. Evidence must be analyzed to be included or excluded considering the clinical question at hand. Validity, importance, and applicability are three points to be appraised given research evidence. External validity considers if the evidence found is applicable and generalizable beyond the limits of the study design. Internal validity determines whether the study was run carefully and according to the study design. Study errors can be because of random errors or because of bias. Bias is anything that produces variation in an estimate either due to poor study design or poor data collection. Selection bias that influences the outcome, or measurement bias that can lead to inaccurate outcomes.

STEP 4: Applying the evidence

The exercise of EBM is put into practice as the integration of the best-appraised evidence with clinical expertise and the patient values. This collaboration is shown in Fig. 3.2. The efficacy of the intervention or the risks associated should be presented and discussed to allow an informed consent or decision.

STEP 5: Evaluating performance

Bringing EBM into regular clinical practice raises the need to keep track of whether its implementation is done correctly or not. Formal auditing of performance can be done to evaluate effectiveness and efficiency in the process.

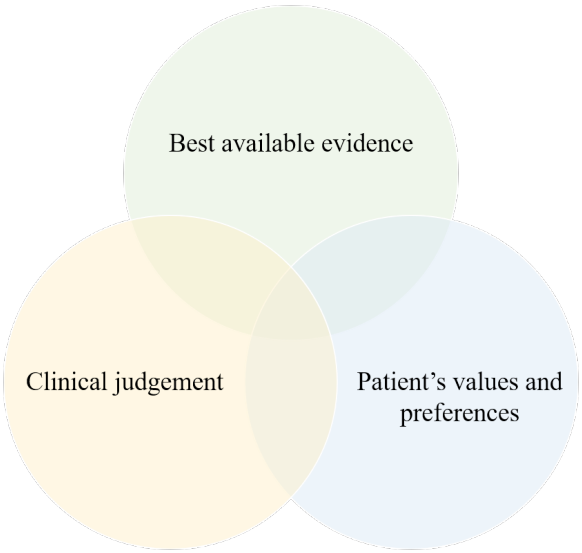

Figure 3.2: Concept of Evidence-based Medicine.

3.2 Shared decision-making

3.2.1 Definition

The clinical decision-making process is ideally the application of the 5 step model of EBM. Health professionals rely on their experience and skills, as well as their teams'. A combination of both experience and skills must be played, together with the best available evidence and the individual patient's concerns and preferences so it is possible to arrive at an informed decision. [26]

Models of decision making are characterized by the roles the clinician and patient take, the sharing of information, the parties that deliberate and the person who makes the final decision.[27] In the paternalistic model, the health professional takes a more active role in assessing and reporting the selected evidence for the best intervention, compared with the patient that only is in a position to accept the proposal. The information flow is one way, from the clinician to the patient and the final decision resides on the clinician. The patient only consents. At the other side, there is the informed medical model. The clinician here has a more passive role of reporting the treatment possibilities without providing their recommendation, whereas the patient receives all information and decides on the intervention without the direct opinion of the health professional.

SDM is a relatively new approach where the decision is made in a collaborative process, and the information flows in two ways. Both the clinician and the patient take active parts in the process. It is defined as *an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences*[28].

The healthcare professional reports the best evidence of different possible interventions, informing about the benefits and harms of each of them, in an accessible format to the patient. The latter shares doubts and concerns, personal circumstances, hopes and expectations. After a discussion, a decision for the best intervention is achieved by both parties.

There are four main principles when one considers SDM:

1. Both healthcare provider and patient are involved in the decision-making process: it is a commitment between the two parties, considering there can be an involvement of family and friends;

2. Both healthcare provider and patient share information: it is a prerequisite that the information should flow in both ways;

3. Both healthcare provider and patient participate in the decision-making process by expressing treatment preferences: benefits and harms, hopes and fears must be considered to weight the different options;

4. Both healthcare provider and patient agree on the treatment to implement: ad agreement must be reached and the responsibility for it mutually accepted by both parties.

3.2.2 The practice of Shared decision-making

There is a considerable amount of literature that defines practical methods to SDM. Provide information and support the decision-making process are the core features of any SDM methodology. To move from initial awareness to an informed preference, the patient needs to communicate and work together with the clinician to deliberate the best choice at hand[9].

The 3 talk model is defined by a set of a choice, option and decision talks. It begins with the choice talk, where the patient is made aware that options exist after the health situation has been described. At this stage, one must ensure that the best evidence and information will be provided, and assess the patient's goals and hopes. The option talk later follows to present which are the treatment options to consider. Harms and benefits of each alternative are explained to the patient, and support is offered to assist in any doubt. The third conversation is where both parties align the initial goals to the preferred option and the patient's informed preferences, and a decision is finally reached.

Another method is the SHARE approach which provides five steps to practice SDM. To seek patient participation (S), helping them to explore and compare options (H), assess the patient's values and preferences (A), to reach a decision (R) and evaluate the decision (E).

By adopting any of the above methods one is able to enhance this approach. It is of most importance to have as a first step the engagement of the patient since they often lack consciousness on all the viable options and look for more information. Therefore, gaining their commitment is a way to reflect their goals and concerns as an important part in decision-making. Secondly, presenting the options and discuss the possibilities with the patient. The constant dialogue helps to build a trustworthy relationship between patient and healthcare professional. The harms and benefits related to each alternative should then be presented and clarified. One should always need to consider the patient's values and preferences as a fourth step, as a way for the clinician to gain knowledge to then contribute with a better guidance. The fifth step lies most on the healthcare professional side, that should be at disposal to facilitate the deliberation and decision making. Last but not least, the implementation of the decision, making plans to review the option in the future, closes the cycle to SDM.

There are four common elements among the various models presented to practice SDM [29]:

- Information: healthcare professionals should provide clear and unbiased information to the patient on their health condition, benefits and harms of each possible intervention options and support an informed decision;
- Support: there is a requirement to support the patient throughout the decision-making process, to gain knowledge and understand the information and to discuss their values and preferences;
- Discussion: information should flow in both ways as the patient and clinician should make the decision together based on the best available evidence and the patient individual characteristics and needs;
- Follow-through: Patients should continue to receive support from the health professional after the final decision has been agreed based on evidence and their values and needs.

3.2.3 Decision aids

It is not an easy endeavour for the patient and the clinician to discuss the various treatment options for a given health condition using the best available evidence and considering the patient's unique context, values and preferences. Healthcare professionals need the soft skills and tools to convey information as clear and precise as the patient has the ability to perceive it. On the other hand, patients need the tools and support to receive and interpret the information as well as have the ability to convey their own values and preferences for discussion.

Decision aids appear as evidence-based tools that provide help to patients, and supplement clinician's counseling, to make deliberated and informed choices[30]. These interventions should present the decision that needs to be considered in an explicit way, by providing the evidence-based information on the health condition at hand, harms and benefits of each options' outcome and help the patient to clarify, based on their values and preferences, the weight on the benefits and harms of each alternative. Patients that use decision aids tend to have a better knowledge and a clearer understanding on their values. They also tend to take a more active role in the decision making process and have a better perception on risks and outcomes.

These tools exist in various formats such as fliers, brochures, visual aids, videos and computer programs. Decision aids may focus on prevention, diagnosis or treatment interventions of health conditions[10].

3.3 Menstrual cycle

Every healthy women consider menstrual periods as a normal part of life. From puberty to menopause, the woman's health, mood and daily living is affected by menstrual cycles. It is thoroughly controlled by a sequence of events that involve the coordination between the hypothalamus, anterior pituitary, ovaries and endometrium. The menstrual cycle is determined by genetic influences, but is also troubled by environmental factors[31].

3.3.1 Phases of the cycle

The reproductive life of women is expected to last an average of 36 years, having its beginning with menarche in adolescence, and ending with menopause. The 28-day cycle is considered the average case, has two main phases, the follicular and the luteal phases [32]. The period, or menstruation, is the main symptom of the existence of a cycle, and normally should occur at the end of the luteal phase and the beginning of the new follicular phase. The release of an egg cell from an ovary to the Fallopian tube, ovulation, occurs after the follicular phase and before the luteal phase. In Fig. 3.3 a diagram of the different phases of the cycle is presented regarding the ovaries and the uterus.

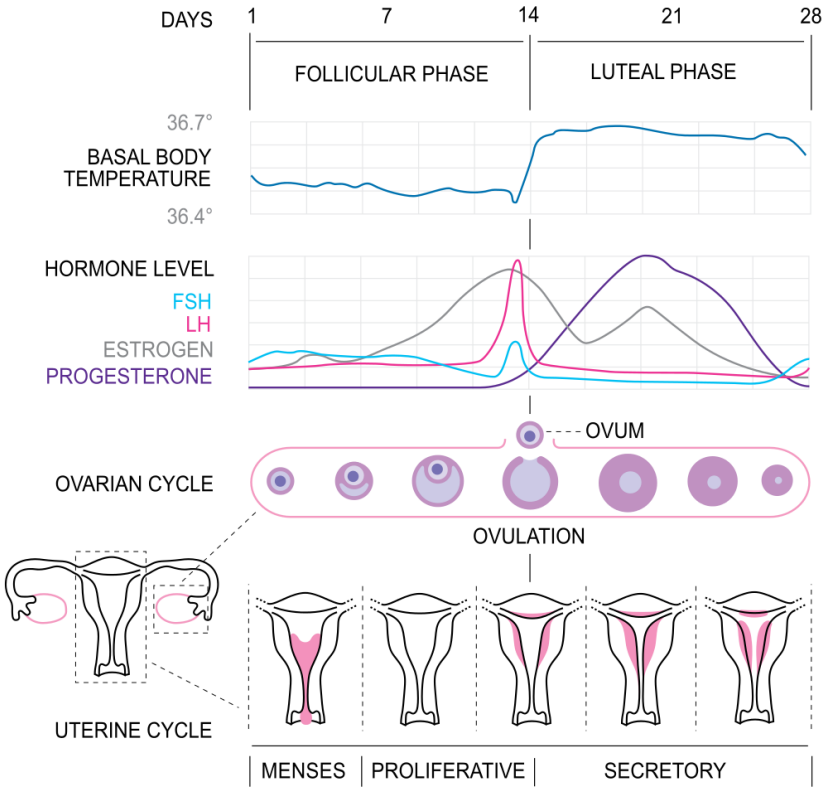

Figure 3.3: Diagram of the menstrual cycle [33].

Phase I - menses and follicular phases

The first day of the cycle begins with menses. It is characterized by the shedding of the inner lining of the endometrium. The menstrual fluid that exits from the vagina is composed of soft tissue and blood vessels [34].

The follicular phase of the ovarian cycle begins with the maturation of the ovarian follicles to later on release an egg.

A regular period can have the duration of 3 to 6 days, but the normal range can go from 2 to 12 days. The blood loss average is 33 milliliters, with a range that can go from 10-84 ml [32]. Women can also experience dysmenorrhea that is characterized by abdominal cramps, and uterine pain, mainly in the first days of menses [34].

Phase II - proliferative and follicular phase

With the beginning of the follicular phase, the endometrium proliferates because of the ovarian follicle activity and maturation. The lining of smooth tissue and blood vessels thickens the uterus, that is preparing for a possible implantation. There is also the production and excretion of cervical mucus by the cervix.

This phase has variable duration that normally can range from 10 to 23 days. This variability is what most influences the cycle length [32].

Phase III - ovulation

Ovulation is the release of the ovum from the matured follicle from the ovary into the Fallopian tube.

Phase IV - secretory and luteal phase

After ovulation, the follicle that released the egg is transformed into the corpus luteum that is responsible to make the endometrium receptive of the fertilized egg in case of fecundation. There is an increase in the blood flow and a reduction in the contractibility of the uterus. This can be noticed externally by a raise in a woman's BBT.

The range of duration of this phase is of 7 to 19 days, with a preponderance of 14 days length [32]. If fecundation does not occur, the corpus luteus degenerates, and the endometrium weakens, giving way to a new cycle with the appearance of menses.

3.3.2 Endocrinology of the cycle

The menstrual cycle is mainly regulated by hormone factors. In Fig. 3.4 a simple overview of the endocrinology of the menstrual cycle is presented.

The hypothalamus stimulates the anterior pituitary by secreting gonadotropin releasing hormone (GnRH). The pituitary secretes both follicle stimulating hormone (FSH) and luteinizing hormone (LH) that regulate the production of steroid hormones by the ovaries [31]. Estrogen and progesterone will induce the proliferation of the endometrium and affect other organs. Steroid hormones will produce a feedback at the level of the anterior pituitary, by inhibiting the secretion of gonadotropins.

The follicular phase of the menstrual cycle is influenced by FSH that is responsible of stimulating a few ovarian follicles, from which one will continue to maturity. As they mature, the follicle will produce and secrete estrogen that causes the lining of the uterus to grow. It also is responsible for the production of cervical mucus.

When the follicle is nearly matured, the levels of estradiol will induce the production of LH, that will lead to ovulation. The pituitary hormones will then cause the follicle to transform into the corpus luteum, that produces progesterone, which will have a negative feedback on the secretion of FSH an LH. During the secretory phase, progesterone makes the endometrium receptive to implantation should fertilization have occurred. If fertilization does not occur, the corpus luteum will atrophy leading to a decrease in progesterone levels. Menses is then triggered and a new cycle begins.

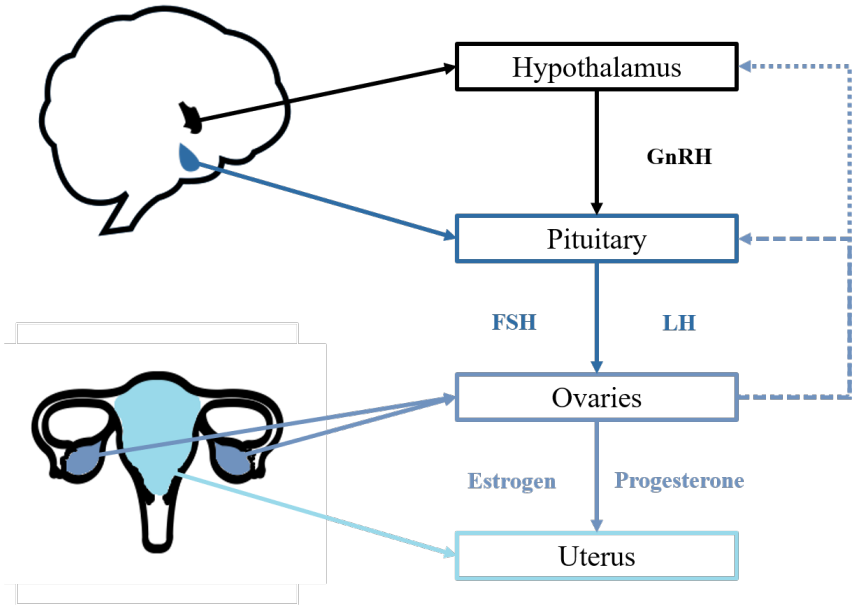

Figure 3.4: Endocrinology of the menstrual cycle.

3.3.3 Biomarkers of the menstrual cycle

Biomarkers are markers of a biological process or state, that can provide information useful to the clinical context. It is a characteristic that can be measured and evaluated objectively. Normal biological processes, pathogenic processes or even pharmacological responses can be studies using biomarkers [35].

The different stages of the menstrual cycle can be assessed from the observation and tracking of biological markers such as cervical secretions, the cycle length or the BBT.

Cervical mucus

Cervical mucus secretions characteristics change throughout the menstrual cycle, given the estrogen and progesterone fluctuations that occur [36]. Prior to ovulation, mucus evolves from a scarce thick constitution. With the increasing levels of estradiol if the follicular phase it evolves to a more fluid and abundant state, that picks in ovulation. Following ovulation, in the luteal phase, the rising levels of progesterone cause the mucus to thicken and decrease [37].

Vaginal bleeding

Vaginal bleeding normally lasts between four and seven days, being more abundant on the first and second days. Volume can vary from 10 to 80 mL, which corresponds to about one to three tablespoons [38].

Basal body temperature

BBT should be measured at rest. If measured at the same time, everyday, it can be used to assess a woman's fertility window. BBT is usually lower in the follicular phase of the cycle, and raises up to 0.6°C in the luteal phase, after ovulation [39].

Table 3.1: Female and male infertility factors [43].

Female infertility	**Male infertility**
ovulation disorders	infection
uterine abnormalities	injury
tubal obstruction	toxin exposure
peritoneal factors	anatomic variances
cervical factors	chromosomal abnormalities
	systemic diseases
	sperm antibodies

Cycle length

Period is the first day of the menstrual cycle. The length of a cycle is highly variable, ranging from 25 to 35 days in women. This is due to the high irregularity of the follicular phase, whereas the luteal phase has a more steady average of 14 days [32].

3.4 Women's health and infertility

Infertility is a disease [40]. It can be defined as the couple's inability to achieve a pregnancy after a reasonable period of time having sexual intercourse without the use of any contraceptive. The incapacity to achieve pregnancy through natural means, sterility, or the failure to proceed with a pregnancy until giving birth to a new born, sub-fertility, can be referred to as infertility.

The period of time up to which the couple is diagnosed as infertile varies from definition to definition. The World Health Organization mention a minimum period of two years, but the majority of healthcare providers consider a couple as being infertile after a year actively trying to achieve pregnancy and not succeeding [41]. Given the age relation with infertility, for couples where the woman is 35 years or older, six months trying to conceive is considered a reasonable period [42].

3.4.1 Causes of infertility

The cause of infertility may dwell on female factors alone, such as ovulatory disorders, low ovarian reserve, anatomical or physiological disturbances of the reproductive system, or other conditions. There are also male factors, that result in infertility, like abnormal semen function, anatomical or physiological disturbances of the reproductive system and other chronic diseases and conditions [40].

Additional risk circumstances like old age, smoking, alcohol abuse and obesity may also have a negative contribution towards low fertility [43]. Table 3.2 summarizes the infertility factors that affect female and male fertility.

A considerable number of infertile couples manifest a combination of both female and male factors. However, for some others with apparently normal reproductive systems and function have unexplained infertility - idiopathic infertility.

Ovarian dysfunction

The most common cause of infertility is the absence of ovulation, anovulation. Ovarian failure to release the oocyte from its follicle can be related to genetic, autoimmune, chemotherapy and other factors. Polycystic ovaries is the most frequent cause of anovulation.

Other causes may derive from a dysfunction secondary to gonadotrophic regulation. Hyperprolactinaemia is the occurrence of high circulating prolactin hormone concentrations. This dysfunction alters the secretion gonadotrophin-releasing hormone (GnRH) and is described by clinical manifestations such as inadequate luteal phase, anovulation and amenorrhoea. Hypogonadotrophic or hypergonadotrophic hypogonadism express low and high levels of FSH and LH hormones, respectively.

The total number of oocytes available to a woman is predetermined in the intermediate months of gestation. Considering ovulation the normality, the ovarian reserve may also decrease throughout the life due to apoptosis and other factors. Age, genetic conditions, autoimmune abnormalities, smoking, ovarian surgery, cancer therapy, endometriosis and others are therefore associated with diminished ovarian reserve [41].

Tubal-peritoneal infertility

Oocyte fertilization occurs at the outer end of the Fallopian tubes. They are also implicated in the action of early embryo development and their transport into the uterine cavity. Infertility may be associated with anatomical abnormalities in the Fallopian tubes. Certain conditions like pelvic adhesions secondary to infections, pelvic inflammatory disease, surgery or endometriosis are in the origin of the tubal-peritoneal factor [41].

Endometriosis

This disease is characterized by the presence of endometrium-like tissue outside the endometrium - uterus. It can be located in other organs such as the ovaries and Fallopian tubes. Endometriosis can affect fertilization by anatomical alterations, anovulation and luteal phase alterations [41].

Uterus dysfunction

Uterine structural or functional abnormalities can be either congenital or acquired. They have been associated with infertility and recurring abortions [41].

Sperm migration disturbance

Soon as the sperm is deposited in the vaginal sac, it contacts the cervical mucus in the cervix and keeps moving upwards the genital tract. The study of sperm migration can determine the quality of the cervical mucus and the semen and any interactions among them. The presence of anti-sperm antibodies or certain pathogenic agents in the cervical mucus influences the sperm motility, having a negative impact in fertility [41].

Male infertility

- Ejaculatory dysfunction: lack of ejaculation, delayed, retrograde or premature ejaculation can be a due to trauma or psychological factors, iatrogenic or pharmacological reasons, inflammation or functional abnormalities [40].

- Varicocele: abnormal dilation in testicular pampiniform plexus - that has the function of venous return from and temperature regulation of the testicles - affecting testicular function and hence spermatogenesis [41].

- Glands infection: infections that affect the prostate, seminal vesicle and epididymis can raise the amount of leukocytes and diminish the number of viable spermatozoa in the semen.

- Systemic and iatrogenic causes: medical intervention related causes, surgery or medication, radiation and high temperature exposure may lead to testicular failure.

Immune infertility

Immune responses in female and male reproductive systems like the development of antibodies that react against spermatozoa interfere with fertility [41].

Genetic infertility

Genetic causes like abnormalities in the sex chromosomes, gene mutations and other though rare can be associated to reproductive disorders.

In women, alterations in the X chromosome, like the Turner Syndrome may result in irregularities in the menstrual cycle. Gene mutations, such as the deletion of the gene ZFX shortens the reproductive life and may lead to premature ovarian failure.

Genetic pathologies in men can be separated into single gene defect and numerical structural chromosomal defects. The genetic abnormality can disturb spermatogenesis, hormone production and physical development [41].

3.4.2 Diagnosis

The couple's inability to achieve pregnancy after a 12 month period having sexual intercourse without the use of any contraceptive heavily suggests infertility. The inquiry towards finding the root of a couple's infertility should start with the medical history of both woman and man. After which a review of systems and physical examinations follows. Evaluation usually begins after 12 months but can begin earlier if there is a heavy suspicion based on medical history or if the woman is older than 35 years [13]. The couple should be examined together and in separate, given that there can be details the other partner is not aware and are more easily shared with the healthcare professional, and specific physical and laboratory examinations.

Evaluation of women infertility

Starting with the medical inquiry, the menstrual cycle history should be assessed, together with contraception use and previous pregnancies and outcomes. Past infections and medication administration should be considered as well as previous surgeries on the reproductive system. Occupational exposure to radiation or dangerous substances and risk behaviours like smoking and substance abuse should also be registered.

The menstrual cycle details can determine whether the cycles are ovulatory or anovulatory [13]. Review of systems and physical examinations or laboratory tests should be run to document ovulation. For regular length periods, the day 21 progesterone level test can easily determine whether it occurs or not. If the progesterone level is below normal, thyroid-stimulating hormone, prolactin, FSH and estradiol analysis is run. If the progesterone level indicates ovulation, tubal or uterine abnormalities should be looked for, through a hysterosalpingography - fluoroscopy procedure to examine the uterus and fallopian tubes - or ultasonography to examine the tubes, uterus and pelvis [43].

The World Health Organization, WHO, groups ovulatory disorders into 3 categories. The first group gathers the hypothalamic pituitary failure causes, that correspond to approximately 10% of registered ovulatory abnormalities. Women in this group repeatedly experience amenorrhea and low gonadotropin levels. Group II corresponds to the gross majority of around 85% of hypothalamic-pituitary-ovarian axis dysfunction. Polycystic ovary syndrome and hyperprolactinaemia are some conditions considered in this group. Ovarian failure characterizes group III. In this cases conception with the woman's own oocyte is greatly improbable to be achieved [43].

Evaluation of men infertility

A man's previous fertility should be considered in the medical history record, alongside prior pelvic or inguinal surgeries, systemic diseases and occupational exposures. As same as with a woman's record, risk behaviours should also be registered, like toxin exposure.

Review of systems and physical examination that follow reside in evaluating the existence of genital infection, hernias or signs of androgen deficiency. The man's testicular mass and varicocele should also be tested [13].

Specialized tests and laboratory assessment follow. A semen analysis should come first. An assessment of the ejaculate characteristic parameters: volume and concentration, pH, spermatozoa vitality, motility and morphology and the presence of other cells [40]. If the results come abnormal, the infertility diagnosis is confirmed. If however the results come normal, new tests should be run to upraise other possible etiologies. Blood analysis for a complete blood cell count, in case infection is suspected, or to examine testosterone levels. Analysis to urine or renal and liver function studies, and ultrasonography to the reproductive system.

3.4.3 Treatment

The therapeutic approach to infertility is determined once its etiology is discovered. Treatment can involve only the man, or only the woman, but more commonly, the couple is involved together.

Regarding male factor infertility, if the semen analysis results are abnormal, the man or couple should be referred to a fertility specialist. Ovulation occurrence evaluation determined the how to proceed when considering female factor infertility. If the phenomenon is not registered, ovulation induction should be considered. If there is a suspicion for anatomic variance or obstruction, recommendation for surgical evaluation and treatment should be made [43].

Assisted reproductive technology

ART comprises treatments and procedures that maneuver human eggs or embryos to help a woman or couple dueling infertility become pregnant.

Interventions are considered in cycles, that begin with the administration of fertility medication or ovaries' motorization for follicle development and maturation. If there is the development of oocytes, the ART procedure can be performed.

Different ART interventions apply to different infertility diagnosis. Male or female gamete retrieval may be required in order to combine the oocyte and sperm to achieve fertilization. The most common procedures are [42]:

- IUI - intrauterine insemination - medical intervention that involves injecting sperm into the uterus of a woman to facilitate fertilization; IUI implies ovulation induction and sperm retrieval, but does not involve the manipulation of oocytes.

- IVF - *in vitro* fertilization - ART procedure that fertilizes an oocyte outside of the woman's body; IVF requires fertility medication for follicle development and maturation, eggs retrieval from the ovaries and sperm retrieval; the resulting embryos are transferred later through the cervix into the woman's uterus.

- ICSI - intracytoplasmatic sperm injection - laboratory procedure where a single sperm cell is injected directly into an oocyte; ICSI requires fertility medication for follicle development and maturation, eggs retrieval from the ovaries, sperm retrieval and selection; the resulting embryos are transferred later through the cervix into the woman's uterus.

The ART technique that best applies to a couple's situation is chosen based on their infertility diagnostic. Table 3.2 presents a few examples on the infertility cause and advised ART treatment.

An ART cycle may accomplish a clinical pregnancy and possibly a live birth. But often they can be canceled or interrupted by a various number of reasons. Procedure difficulties like inability to obtain matured follicles, failure to complete a pregnancy until term, patient illness or decision to stop the cycle.

Table 3.2: Infertility cause and recommended ART procedure.

Infertility cause	**ART procedure**
low ovarian reserve	IVF (with donated oocytes)
tubal cause	IVF
uterine cause	IUI
endometriosis	IVF
male factor infertility	ICSI
idiopathic cause	IVF/IUI

3.5 Summary

EBM can be defined as the integration of the best quality evidence, the clinician's expertise and knowledge and consideration for the patient's values and preferences. Nowadays there is an enormous amount of medical literature, and healthcare professionals often lack time to follow the state-of-art of current evidence on specific research questions. Keeping track of published articles to critically appraise useful evidence can be achieved by recurring to systematic reviews, meta-analysis and clinical practice guidelines [18]. The specific circumstances where the studies are performed lead to findings and conclusions off from a real-life situation. To extrapolate conclusions to apply in EBM one needs the judgment from experience of healthcare professionals and the patient's background. There is a need to bring out the patient's values and find a way to combine them into clinical decision-making. Rational clinical decisions need to be consistent with personal hopes, goals, expectations, predispositions, beliefs, politics and religion [5].

The clinical decision-making process is ideally the application of the 5 step model of EBM. SDM is a relatively new approach and it is defined as *an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences*[28]. Four elements are required to practice SDM [29]. Clear and unbiased information that clinicians should provide the patient. They also require Support throughout the decision-making process, to gain knowledge and understand the information and to discuss their values and preferences. Discussion between the patient and clinician should in order to the decision together based on the best available evidence and the patient individual characteristics and needs. And finally, Follow-through agreement, since patients should continue to receive support from the health professional.

Every healthy woman should consider menstrual periods as a normal part of life. It is controlled by a sequence of events that involve the coordination between the hypothalamus, anterior pituitary, ovaries and endometrium. The 28-day cycle is considered the average case, has two main phases, the follicular and the luteal phases [32]. Period, or menstruation, is the main symptom. The release of an egg cell from an ovary to the Fallopian tube, ovulation, occurs after the follicular phase and before the luteal phase. The menstrual cycle is mainly regulated by hormone factors, FSH, responsible of stimulating ovarian follicles, than secrete estrogen, and luteinizing hormone, LH, that leads to ovulation and the transformation into the corpus luteum that produces progesterone. The different stages of the menstrual cycle can be assessed from the observation and tracking of biological markers such as cervical secretions, the cycle length or the BBT.

Infertility can be defined as the couple's inability to achieve pregnant after a reasonable period of time

having sexual intercourse without the use of any contraceptive. The causes may dwell on female factors like ovulatory disorders, low ovarian reserve, anatomical or physiological disturbances of the reproductive system, or other conditions. But are also male factors such as abnormal semen function, anatomical or physiological disturbances of the reproductive system and other chronic diseases and conditions [40]. The therapeutic approach to infertility is determined once its etiology is discovered. ART comprises treatments and procedures that manoeuvre human eggs or embryos to help a woman or couple duelling infertility become pregnant.

Chapter 4

Fertility*Care*

In this chapter, the CrM Fertility*Care*™ system is presented as the Case study. More specifically Fertility*Care* Portugal. Its history and and the description of the system structure and ways of exercise.

Natural Procreative Technology is also presented as a health science that aims to monitor and maintain a woman's reproductive and gynecological health,by providing medical and surgical treatments that cooperate with the woman's reproductive system [44].

4.1 History

Due to the arrival of the oral contraceptive in the 1960s, the legalization of induced abortion and the development of artificial reproductive technology procedures, the obstetrician-gynaecologists have adapted their practice. Focusing on contraception, abortion, sterilization and ARTs, the literature and research towards classifying the underlying causes of gynecological conditions and infertility has been somehow neglected.

Research on the normal and abnormal states of the woman's fertility cycle are at the basis of the creation of the CrM Fertility*Care* System by the medical Dr. Thomas Hilgers and his coworkers began in 1976, in the Creighton University, USA. The System became fully described later on 1980. Furthermore, until the present investigation still continues.

It started in Omaha, Nebraska and soon expanded to Canada and Europe, to countries such as the United Kingdom, France, Netherlands, Switzerland, Poland, Ireland and others [45]. There are also Fertility*Care* centers in Africa, Asia and Oceania. Figure 4.1 displays the distribution of centers in all continents.

4.1.1 Fertility*Care* Portugal

Fertility*Care* arrived to Portugal through nurse Vanessa Machado that first finished the teacher training program in 2013/15. The team is formed by Practitioners, currently three nurses, and Medical consultants, currently two medical doctors.

Figure 4.1: World distribution of Fertility*Care* centers.

Located in the Lisbon district, it has now expanded to Porto, Braga and Viseu, having reached more than 500 people, among women and couples.

4.2 Creighton model system

The CrM system is based on the standardized observation and charting of the biomarkers to assess a women's health and fertility. Its areas of intervention are infertility, spontaneous recurring abortion, family planning and woman's health.

Women or couples can use this method as a family planning approach to evaluate the natural fertile and infertile periods of the cycle. And, through the charting of biological markers it is possible to discover and track abnormalities in a woman's health.

CrM system relies upon a woman or couple's understanding on the presence or absence of the cervical mucus as a determinant of fertility. To this purpose, there is a standard teaching set-up and language to classify the biological markers. Natural family planning accredited practitioners follow and advise each woman or couple on the method and the ways to record their biomarkers [46].

The CrM Fertility*Care* System is supported by a thorough ongoing research, accredited teaching programs for the healthcare professionals and standard teaching format throughout its centres of practice.

Introductory session

Couples or women that are interested in entering this program register for the first introductory session. It is a one-hour presentation where a Fertility*Care* qualified healthcare professional presents the CrM method. They provide a simple and clear scientific insight on the anatomy and physiology that support the model and provide information on the more technical aspects of charting the biomarkers of the women's fertility cycle.

After the session, those who have the interest to enter the program, are provided with a user manual, a fertility charts and monitoring stamps and a follow-up form they should fill to the first session appointment, that should be scheduled two weeks after the introductory session.

Follow-up sessions

The full program suggests that there should be eight follow-up sessions in a one-year period. The first four should be done in a two-week base, the fifth one month later and the last three every three months. These sessions are set in a standardized way, where the Fertility*Care* practitioner or the NaPro medical consultant should go through a 26-page charting form, and a case management book as an aid for the observations according to the different reproductive classification of the woman or couple.

The main objective of these follow-up sessions are the graphic chart revision, and observation registry, NaProtracking (explored in the following section 4.3) and referral to a Napro medical consultant in case of abnormal values. Support any doubts or concerns the woman or couple might have, and work on their motivation on keeping track of their health and relation.

Measurements will differ among women in different health situations. Reproductive classification is based on whether a woman has regular, short or long cycles, or if she is breast feeding, weaning, leaving the pill, in a pre-menopausal situation, post-partum but not breast feeding, post abortion, or even in case of infertility or pregnancy.

Evaluation

Every step of the CrM should be assessed. Each introductory session is evaluated by the attending couples, and in the 4th, 5th and 6th follow-up sessions, a standardized evaluation form is provided for the woman or couple to evaluate the teacher.

The couple's knowledge if the model is also evaluated through a true/false series questionnaire. At the end of every appointment, the couple is invited to judge their level of satisfaction, confidence and receptivity to a pregnancy.

Teacher training program

Each Fertility*Care* practitioner and NaPro medical consultant needs to attend a one-year training program to be a certified CrM teacher. This should be certified by the American Academy of Fertility*Care* Professionals.

4.3 Natural Procreative Technology

Natural Procreative technology (NaProTECHNOLOGY) has the CrM as the basis to monitor the reproductive and gynaecologic health of couples and women. Various are the applications of NaProTECHNOLOGY, that from the menstrual and fertility cycle, can target, diagnose and treat disorders and assist couples in family planning and infertility, and women's health monitoring.

Biomarkers can be observed and recorded in a standardized, prospective and reproducible manner. The length of the cycle, pre- and post- Peak-day phases, the mucus cycle measurements, Peak day occurrence and length of menses, can be gathered and combined for a deeper understanding of the menstrual and fertility cycles, and the irregularities that can be associated with them [47].

Family Planning and Infertility

The basic charting of the observable biomarkers by the CrM System and Practitioner counseling can guide a fertile couple in their family planning. Through daily recordings and mucus examination, the woman or couple can select the most fertile and infertile days, according to their intention to achieve or not a pregnancy. It can be used by any fertile woman with regular or irregular cycles, breast-feeding, pre-menopausal or post-pill. When used correctly and according to the practitioners instructions, CrM System efficacy to avoid pregnancy is higher than 95% [48].

Associating CrM charting patterns with other diagnostic procedures like ultrasound, hormone assessment, diagnostic laparoscopy or hysteroscopy may identify many conditions related to infertility.

Hormonal assessment of the menstrual cycle

By ordering a day 22 progesterone level test, the NaPro medical consultant can evaluate and diagnose the follicular and luteal functions [47].

The correlation between the estrogen levels and the secretion of cervical mucus has been an object of deep investigation. By assessing the discharge patterns, significant changes are associated with specific types of conditions. For instance, infertile women with regular cycles, endometriosis or polycystic ovaries register a considerable decrease in mucus secretion. Also, reduction in mucus is due to decreased levels of estradiol.

Disorders of ovulation

Alterations in mucus secretion are associated with abnormal hormone production from either the follicle and the corpus luteum. Ovulation disorders can be identified from the CrM charting of the mucus cycle. The comparison of the mucus discharge patterns of fertile patients, to the ones of those with ovulation cycle abnormalities shows a considerable decrease or alteration of the latter. Luteinized unruptured follicle syndrome and affolicularism, immature follicles and empty follicle syndrome can be diagnosed through a transabdominal or transvaginal ultrassound procedure.

Progesterone replacement therapy

The corpus luteum function can be easily evaluated through the charting of the mucus cycle. Post-ovulatory phase can be identified and assessed independently of the cycles being short or long. A decrease in progesterone levels may result from abnormalities pf the corpus luteum function. A therapeutic procedure to this case is progesterone administration in the post-Peak phase of the cycle.

Pre-menstrual syndrome and Post-partum depression

Pre-menstrual syndrome is associated with a considerable decrease in progesterone production. Progesterone replacement therapy or administration of human chorionic gonadotropin, hCG, has shown to be more beneficial than fluoxetine treatment. Progesterone replacement therapy can also be considered as a treatment to decrease the symptoms of post-partum depression [47].

Unusual bleeding

The CrM charting may bring to evidence unusual bleeding occurrences. Heavy menstrual periods and continuous bleeding, pre- or post-menstrual bleeding can be measured and so help to identify different conditions, like endometriosis.

4.4 Summary

Research on the normal and abnormal states of the woman's fertility cycle are at the basis of the creation of the CrM Fertility*Care* System by the medical Dr. Thomas Hilgers. The CrM system is based on the standardized observation and charting of the presence or absence of the cervical mucus as a determinant of fertility the biomarkers to assess a women's health and fertility. Its areas of intervention are infertility, spontaneous recurring abortion, family planning and woman's health.

Couples or women that are interested in entering this program register for the first introductory session. The full program suggests that there should be a series of follow-up sessions in a standardized way, where the Fertility*Care* practitioner or the NaPro medical consultant should go through the chart and the observations according to the different reproductive classification of the woman or couple. The couple's knowledge if the model is also evaluated and at the end of every appointment, the couple is invited to judge their level of satisfaction, confidence and receptivity to a pregnancy.

Natural Procreative technology has the CrM as the basis that from the menstrual and fertility cycle, can target, diagnose and treat disorders and assist couples in family planning and infertility, and women's health monitoring.

Chapter 5

Data research and methods

The objective of the present dissertation is to assess Fertility*Care* as a Shared decision-making approach to reproductive and reparative medicine. A qualitative evaluation of whether or not Fertility*Care* respects the concept of EBM will be developed. Following that, the 9-item shared decision-making questionnaire, SDM-Q-9, will be administrated to all women and couples that enrolled in the project. This will be performed in order to appraise the Participants perception of SDM.

5.1 The 9-item shared decision-making questionnaire

Shared decision-making is defined as a cooperative practice where both patient and physician actively share information to reach an agreed decision. The measurement of the practical applications of SDM is a challenge, given the different processes there are to this practice.

SDM measurement tools have been developed to evaluate its process from the perspective of either the patient, healthcare professional or sometimes an external observer [49]. These approaches aim to provide the interdependent decision construct between the parties.

Among the variety of instruments that measure the different aspects of SDM, only a small number have undergone rigorous psychometric testing to measure individuals' mental capabilities and behaviours. Examples are the Decisional Conflict Scale - DCS - to measure uncertainty in decision making, or the OPTION scale that measures the overall shared decision-making process through observation techniques [50]. However, the 9-item shared decision making questionnaire (SDM-q-9) presents itself as a psychometric self-assessment tool developed to measure the practice of SDM from the patient's perspective.

SDM-Q-9 is a variant from an original instrument SDM-Q - shared decision-making questionnaire - that was developed from 2001 to 2005 by a German research consortium on SDM developed an instrument to measure the exercise of SDM [51].

5.1.1 Questionnaire structure and implementation

SDM-Q-9 is based on the essential elements of the Makoul and Clayman's integrated model of SDM [52]:

- Define and explain the medical condition, disclosing that a decision needs to be made;

- Present and discuss the existence of different options;
- Explain the risks and benefits of each option, arguing the pros and cons of each alternative;
- Discuss the patient's values and preferences, given the different perspectives they may have on the relative importance of each possible choice, taking into consideration ideas, concerns and expectations;
- Consider the physician's knowledge and recommendations in the clinical context of the decision at hand;
- Discuss the ability of the patient to follow through with the plan that is going to be laid out - *self-efficacy*;
- Clarify any doubts at a regular basis, checking the patient's understanding of facts and the clinicians comprehension of perspectives;
- Make the decision, acknowledging that sometimes no decision is made or it may be postponed for a later time;
- Organize a follow-up to accompany the outcome of the decision or work further so a decision can be reached.

The SDM-Q-9 was developed to measure the extent to which patients are involved in the decision-making process in a clinical context. Another version exists the perspective of the healthcare professional, the SDM-Q-Doc. The questionnaire is available in different languages, namely Portuguese and English [53].

The model presents nine statements to be rated on a six-degree scale - from *completely disagree* to *completely agree*. The questionnaire usually begins with two or a few more open questions that intend to explore the context of the decision. These are not necessarily part of the instrument, but is considered useful to the process. Figure 5.1 presents the standard model of the SDM-Q-9, providing an example of two possible open questions to start the inquiry.

A score is attributed to each scale degree. Starting with zero (0) for the *completely disagree*, one (1) for the *strongly disagree* and going up to five (5) for the *completely agree* degree. The degrees given on all the nine items are transposed into rates that are summed up to obtain a raw score (RS), that can range from 0 to the maximum of 45 points. A transformed score (TS), ranging from 0 to 100, can be considered, so the process can be more intuitively interpreted. This can be achieved simply by multiplying the RS by 20/9. Zero will indicate the lowest level of SDM, whereas 100 expresses the highest level of shared decision-making. Surely there cannot be a short-sighted interpretation of *the higher the score, the better the SDM model* given the specificity of each medical decision scenario.

Validity and acceptance of the SDM-Q-9

A systematic review was performed in order to examine the use of the SDM-Q-9 in clinical settings and assess the methodological quality of the developed studies. The questionnaire was used in studies which purpose was to evaluate interventions facilitating SDM, but mainly used in training programs and in

Nine statements related to the decision-making in your consultation are listed below. For each statement please indicate how much you agree or disagree.

1. My doctor made clear that a decision needs to be made.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	
2. My doctor wanted to know exactly how I want to be involved in making the decision.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	
3. My doctor told me that there are different options for treating my medical condition.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	
4. My doctor precisely explained the advantages and disadvantages of the treatment options.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	
5. My doctor helped me understand all the information.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	
6. My doctor asked me which treatment option I prefer.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	
7. My doctor and I thoroughly weighed the different treatment options.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	
8. My doctor and I selected a treatment option together.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	
9. My doctor and I reached an agreement on how to proceed.						
completely disagree	strongly disagree	somewhat disagree	somewhat agree	strongly agree	completely agree	
❑	❑	❑	❑	❑	❑	

Figure 5.1: The 9-item Shared Decision-making Questionnaire [49].

Decision aids [54]. The questionnaire has shown to be acceptable, reliable and have factorial validity. The fact that it is translated into different languages makes it possible to compare research studies across nations [55]. However, noticeably this is a relatively young instrument, so there is still some lack of published data.

5.2 Case study

The SDM-Q-9 form was the adopted approach to evaluate the Fertility *Care* program as a shared decision-making practice.

5.2.1 Invitation of participants

In order to reach all possible women and couples in the program, the questionnaire was sent via e-mail. The practitioners and medical consultants provided their applicant e-mail contact list and an online form was developed.

The e-mail presented the dissertation title and explained the purpose of the case study. Participants were asked to give their consent, and were guaranteed the anonymity of their answers and information. If they gave their consent, the form proceeded to the SDM-Q-9. Participants had the freedom to withdraw their consent, or change their answers at any given time the form was open to receive answers.

5.2.2 Questionnaire form structure

Two questions were presented to provide more context to the participant of the questionnaire that would follow:

1. Participants were asked to present the purpose of their last appointment with the Fertility*Care* practitioner/medical advisor.

2. Participants were asked whether any decision was made or reconsidered.

By advising the participants to consider their last follow-up appointments, they were asked to evaluate the nine statements referring to the Fertility*Care* as an approach to clinical decision-making. Questions were presented as exemplified in Figure 5.1. Portuguese was the language used for the survey.

5.3 Data treatment and analysis

General results from the participants will be displayed and described by Frequency analysis. For assessment of the orientation of item-by-item scores, the scores were separated into two categories. Scores from $0-2$ were grouped as "Disagree" and scores from $3-5$ were grouped as"Agree".

From the two first context questions in the questionnaire, it is possible to define groups that can be compared and analysed in order to assess perceptions of shared decision-making.

First question separates participants by different appointment purposes. Such as contrast health situation, classification and women's and couples intention to engage with Fertility*Care*. Since more that two types of groups are to be compared and analysed, data is ordinal and the sample size is not grand, the Kruskal-Wallis test, H test, will be considered.

Second question inquires participants of whether a decision was discussed or reconsidered. Answers of Yes or No create two groups, that will answer the SDM-Q-9 with different perceptions. To compare these responses, the Mann-Whitney U test will be considered. Also, comparisons among groups with different consultation purposes can be performed.

5.3.1 Frequency analysis

The frequency analysis is used as a step to describe the results that were obtained. This is achieved through analysis of the number of occurrences and considering measures of central tendency, spread and variability of the data set and also percentile values.

Mean, median and mode are the most common measures of central tendency. The average value of the data set is the definition of mean. The median states the middle value observed, that is, the number of values below and above the median are the same. The observation that occurs the most number of times is the mode.

The analysis of spread and dispersion of the data gathered are the variance, standard deviation and range. Last but not least, percentile values shows what percent of values in a data set of observations fall below a certain percent threshold.

5.3.2 Kruskal-Wallis test - H test

The Kruskal-Wallis test is a non-parametric test used instead of a one-way Analysis of Variance, since it can consider more than two independent samples. To consider the different small sample sizes and their non-symmetric behaviour we can opt for the H test [56].

The test is characterized by independent group samples, randomized and ordinal data. Also, no assumptions on the underlying distribution are to be made and each independent group has at least five elements. No confidence intervals will exist since no population parameters are estimated.

The H test is usually performed in order to answer the question of whether any difference exists between a set of more than 2 groups at a given significance level α. To execute the test one must first define the Null and Alternative Hypothesis. Decide the α and define the degrees of freedom of the model are the next steps to the state the Decision Rule. The statistical test can then be performed and the results presented and the conclusions driven.

Define the Null and Alternative Hypothesis

The null hypothesis to be tested is that the populations from each group are equal in the sense that no group is dominant over any other. That is, there is no difference between each group. Therefore, the alternative hypothesis states that there is at least one group that is dominant over the other. Hence, there is at least a difference between groups.

H_0 : There is no difference between each group.

H_1 : There is at least a difference between groups.

Define the alpha and the degrees of freedom

The significance level, denoted by α is the probability of rejecting the null hypothesis H_0 when it is true. Stating the $\alpha = 0.05$ will indicate a risk of 5% of reaching the conclusion that there is a difference among groups when in fact there is none.

The degrees of freedom, will be defined by $df = k - 1$, where k is the total number of groups.

State the Decision Rule

For the Decision Rule to be defined, one needs to state the Critical Value. That is the minimum value the test statistic must exceed for the null hypothesis, H_0, to be rejected. Given the test at hand, that can be achieved by use of the Critical Value χ^2 table using the value of α and the number of df as reference.

Calculate the H test statistic

Given the ordinal data, the first thing to do is to rank each of the raw scores of the groups. Then, sum the rank of each group. From that information and the previous steps it is now possible to calculate H.

$$H = \frac{12}{n(n+1)} \sum_{j=1}^{k} \frac{R_j^2}{n_j} - 3(n+1) \tag{5.1}$$

The k is the number of groups, the n_j is the size of the jth group, R_j is the rank sum of the jth group and n is the total sample size.

$$n = \sum_{j=1}^{k} n_j \tag{5.2}$$

The distribution of the Kruskal-Wallis H test statistic approaches a χ^2 distribution with $k-1$ degrees of freedom, df, provided that the minimal number of observations in each group is $n_j \geq 5$. So, if the H value is greater than the Critical χ^2 value, then one can reject the null hypothesis H_0.

5.3.3 Mann-Whitney U test

The Mann–Whitney U test, also called the Mann–Whitney–Wilcoxon test is a non-parametric test that appears as an alternative to the Student's t-test. Because the t-test assumes normal sample distribution, the U test does not rely on distributional assumptions. The test is characterized by independent group random observations and ordinal data. It is used to test the Null Hypothesis that the medians of both samples are the same [57].

The implementation the U test follows the same steps that were previously presented. The first step to execute the test is to define the Null and Alternative Hypothesis. Decide the α and define the degrees of freedom of the model are the next steps to the state the Decision Rule. The statistical test can then be performed and the results presented and the conclusions driven.

Define the Null and Alternative Hypothesis

The null hypothesis to be tested is that there is no difference between the ranks of each sample. That is, the two groups are similar. The Alternative hypothesis will state that there is a difference between the groups.

H_0 : There is no difference between the ranks of each sample.

H_1 : There is a difference between groups.

Define the alpha

The significance level, denoted by α is the probability of rejecting the null hypothesis H_0 when it is true. Stating the $\alpha = 0.05$ will indicate a risk of 5% of reaching the conclusion that there is a difference among groups when in fact there is none.

State the Decision Rule

For the Decision Rule to be defined, one needs to state the Critical Value. That is the obtained U_{obt} value should be equal or less than the critical U_{cri} for the null hypothesis, H_0, to be rejected. Given the test at hand, that can be achieved by use of the Critical U Values for the Mann-Whitney test at the α level of significance.

Calculate the U test statistic

Given the ordinal data, the first thing to do is to rank each of the raw scores of the samples. The lowest score gets a rank of 1, the second a rank of 2 and so on. Then, the ranks of each group are summed up.

For the test statistics, considering n_1 the size of sample one and n_2 the size of the second sample, R_1 is the rank sum of the first sample and R_2 the rank sum of the second group. From that it is possible to calculate U_1 and U_2.

$$U_1 = n_1 n_2 + \frac{n_1(n_1+1)}{2} - R_1 \tag{5.3a}$$

$$U_2 = n_1 n_2 + \frac{n_2(n_2+1)}{2} - R_2 \tag{5.3b}$$

The values obtained by the equations 5.3a and 5.3b should respect the property 5.4.

$$U_1 + U_2 = n_1 n_2 \tag{5.4}$$

From the information previously presented in the previous steps and the equations 5.3a and 5.3b it is now possible to get U.

$$U = min(U_1, U_2) \tag{5.5}$$

Approximation to a Normal distribution

If the number of scores is higher than 10, one can assume that the sampling distribution is roughly normal [57]. That is, for n_1 and n_2 large enough, the U test statistic has approximately a normal distribution $N(\mu, \sigma)$, where μ is the mean and σ represents the standard deviation. Mean and variance, σ^2, are then calculated with 5.6a and 5.6b.

$$\mu = \frac{n_1 n_2}{2} \tag{5.6a}$$

$$\sigma^2 = \frac{n_1 n_2 (n_1 + n_2 + 1)}{12} \tag{5.6b}$$

Notice that this is an approximation of a discrete distribution via a continuous one by application of a continuity correction using a z-score 5.7. From the z-score it is then possible to get the p-value, from which significance can be extracted if its value is lower comparing with the significance level α.

$$z = \frac{|U - \mu| - 0,5}{\sigma} \tag{5.7}$$

Effect size

Effect is the significance of the size of variance, i.e. quantifying the relationship between two groups. One advantage is the fact that this measure is independent of the sample size. Noticeably, with very large samples, the smallest value can result in the rejection of H_0. The effect may be *significant* but not *large*

[58].

For the Mann-Whitney test, effect size can be calculated using 5.8, where z is the z-score, and n_1 and n_2 are the size of each group.

$$r = \frac{z}{\sqrt{n_1 + n_2}} \tag{5.8}$$

One can consider another measure for effect size, presented in 5.9, where p represents the probability that a score collected from $groupA$ will be greater than a score randomly collected from $groupB$. Here, $groupA$ correspond to the group with higher value. The higher the p the larger the effect.

$$p = \frac{U}{n_1 n_2} \tag{5.9}$$

Chapter 6

Analysis and discussion of results

The main objective of this dissertation is to assess Fertility*Care* as a Shared decision-making practice, evidence-based reproductive and reparative medicine approach.

From the definition of EBM, one can evaluate qualitatively whether or not Fertility*Care* respects its concept. Following that, perceptions of Shared decision-making are evaluated by administration of the SDM-Q-9 to all women and couples that enrolled in the project.

There is also the objective of presenting this project as a FABM for women and couples that experience infertility, spontaneous recurring miscarriage, or intend to find a family planning approach not based on artificial contraception or are even just checking their own health.

6.1 Evidence-based Fertility*Care*

The exercise of EBM is the integration of the best-appraised evidence with clinical expertise and the patient values and preferences. The CrM Fertility*Care* System^{TM} is built on research developed through the last decades, an education system designed to assure the quality of service from the instructors and medical advisors, and service to the women and couples.

Scientific foundations and academic literature support the concepts of CrM system and NaProTECHNOLOGY. Efficacy studies have been published showing positive outcomes from the treatment of Infertility with NaProTECHNOLOGY [48]. And meta-analysis have been performed to assess use-effectiveness of the CrM system for family planning, to avoid pregnancy [46]. Success cases either regarding women's health or a couples infertility or even family planning intentions are reported in each of the centers spread through the globe 4.1. However, a systematic review or a database between centers could be created in order to have a common place for the share of information.

CrM education programs have been promoted for more than 40 years. The course is built in order to equip health professionals with comprehensive and professional education, with the aim of providing the best service with the most appropriate clinical judgement. The education target is physicians, nurses, midwives and pharmacists.

Last but not least, patient's values and preferences are at the focus of Fertility*Care* service. All the

follow-up sessions are to support any doubts or concerns the woman or couple might have, and work on their motivation to keep track of their health and relation.

6.2 Fertility*Care* as a Shared decision-making approach

6.2.1 Participants

The questionnaire was sent to 270 women and couples that are or had been engaged with Fertility*Care*. The emails were sent in the beginning of July. A total of 61 answers were collected until the beginning of October.

Purpose of the last appointment

Considering the first part of the questionnaire, participants were asked to present the purpose of the last follow-up session and to remember if any decision was discussed or revised. Their answers are presented in Table 6.1.

Table 6.1: Consultation purpose of the last appointment with the Fertility*Care* practitioner or medical advisor. Participants answer on whether a decision was discussed.

Consultation purpose		Percentage
Follow-up	17	28%
Post-partum	7	11%
Family planning	25	41%
Infertility	10	16%
Pregnancy	2	3%

Decision was discussed?		Percentage
Yes	48	79%
No	13	21%
	Total	61

Five consultation purposes were registered. The majority of women and couples that took the SDM-Q-9, corresponding to 41% of the participants, stated that the last follow-up session was to review their Family planning approach, either to get pregnant or to avoid a pregnancy. For 16% of women and couples that attended the Fertility*Care* follow-up sessions, was to follow and investigate Infertility causes. General follow-up consultations to revise the charting method with the practitioners or medical advisors were registered by 28% of participants, and Post-partum follow-up appointments by 11% of women. Two pregnant women, 3%, attended the follow-up consultation. Regarding the question of whether a decision was discussed or revised, 79% of the participants acquiesced and the rest understood that no decision was considered in their last appointment.

Both questions were intended so participants could remember and prepare their responses for the SDM-Q-9. This with the end purpose of assessing their perceptions of Shared decision-making through the Fertility*Care* program.

6.2.2 Descriptive analysis of the 9-item shared decision-making questionnaire

Items of shared decision making according to Makoul and Clayman's integrated model of SDM [52] are described in Section 5.1.1. But for clarity reasons and to interpret the results from the SDM-Q-9 survey,

the basic content for each item in shared decision-making is presented in Table 6.2.

The initial items, I and II, relate to the steps where healthcare professional express that a decision needs to be made, and enquire the person on their willingness to take part in the decision making process. Intermediate items in the survey, from III to VII, cover the stages where options are presented, outcomes discussed, and patient preferences raised and taken into consideration. It also includes the negotiation on the different intervention alternatives. The VIII step is the decision made by both the individual and clinician and the IX is the final step where the party agrees on the follow-up of the procedure.

Table 6.2: Contents of each step in the practice of Shared decision-making and the related SDM-Q-9 survey items [59].

	Contents
I.	Recognizing that a decision needs to be made
II.	Asking for preferred involvement in decision-making
III.	Informing that different options are available
IV.	Explaining the advantages and disadvantages of the options
V.	Helping to understand the information
VI.	Asking for preferred option
VII.	Weighing the options (doctor and patient)
VIII.	Selecting an option (doctor and patient)
IX.	Agreeing on how to proceed (doctor and patient)

Perceptions of SDM based on appointment purpose

The average RS and TS results from the participants in general, and separating the grades by consultation intent are presented in Table 6.3. The average SDM-Q-9 TS was of $83,3$, from a range of 0 to 100.

By isolating the results by consultation purpose, differences in SDM perception become more clear. Apart from the women who were pregnant that presented the top score of 100, the highest TS of 92, from a range of 69 to 100, was obtained from the group which last consultation purpose was Family planning. Following the Post-partum follow-up group, that gave an average TS of $85,1$. From the group that attended the consultation as a general Follow-up to revise the charting method, the average TS obtained was $76,1$, from a range of 27 to 100. The lowest TS was collected by the women and couples that were in the Fertility*Care* program because they were infertile. From a range of 24 to 96, their average TS was $68,7$.

Differences in consultation purpose

A second analysis was performed in order to determine the orientation of the major differences among groups with different consultation purposes. That is, the level of agreement among the groups in item-by-item of the SDM practice. With this purpose, agreement scores were separated into two categories: from $0-2$ *disagree*, and from $3-5$ *agree*. Every item of the SDM-Q-9 was then summarized into one of these two grades. Results can be found in Table 6.4. Notice that Pregnancy follow-up was not considered due to the low number of answers.

Considering the TS's, there were small differences among groups with different appointment purposes. Family planning group, with a TS of $92,0$ presented a high level of agreement through all steps of the

Table 6.3: SDM-Q-9 average Raw score (RS) and Transformed score (TS). Item-by-item average results from all Participants (General), and considering the purpose of the appointment with the Fertility*Care* instructor: Follow-up, Family planning, Post-partum follow-up, Infertility and Pregnancy follow-up.

	General	**Follow-up**	**Family planning**	**Post-partum**	**Infertility**	**Pregnancy**
I.	**4,1**	4,1	4,6	4,1	2,7	5,0
II.	**4,2**	3,9	4,7	4,3	3,5	5,0
III.	**4,0**	3,4	4,3	4,3	3,9	5,0
IV.	**4,2**	3,6	4,6	4,3	3,8	5,0
V.	**4,7**	4,6	4,8	4,3	4,5	5,0
VI.	**4,1**	3,6	4,7	4,3	3,3	5,0
VII.	**4,0**	3,6	4,4	4,3	3,0	5,0
VIII.	**3,9**	3,6	4,6	4,1	2,4	5,0
IX.	**4,3**	3,9	4,6	4,3	3,8	5,0
RS	**37,5**	34,3	41,4	38,3	30,9	45,0
TS	**83,3**	76,1	92,0	85,1	68,7	100,0

decision-making process. Post-partum follow-up group had the same level of agreement in all items, but in average, 13% lower than the Family planning group.

The group that attended Fertility*Care* follow-up session just to monitor women's health presented high levels of agreement. However, almost 20% disagreed on the intermediate levels of the SDM-Q-9, III, IV and VI. In these steps, different intervention options to the condition at hand are to be presented along with the benefits and disadvantages of each. And also, the discussion on the preferred option of the individual is to be considered.

The group that had more considerable levels of disagreement was the one were the consultation purpose was Infertility. Given the first statement where the healthcare provider discloses that a decision needs to be made, there was a 30% disagreement. Negotiation items of the SDM-Q-9, VII and VIII, had just 60% of agreement. Weighting the different options at hand and reaching a decision together considering the situation of this group were presented as more delicate steps to pursue.

Nonetheless, considering all groups, the highest level of agreement was obtained for the V item, where the health professional should help the individual understand all information. On a General perspective, it had a 98% levels of agreement.

Statistical Analysis

A analysis was performed by performing a Kruskal-Wallis H test on the different consultation purpose groups. Since Pregnancy follow-up group only gathered a total of two answers, the group was not considered for the test. The H test provided a strong evidence of a difference ($H = 11,65$; $p = 0,00869$ at a significance level of $\alpha = 0,05$) between the ranks of at least one pair of groups.

In order to identify which pair of groups presented significant differences, Mann-Whitney U tests were performed on the six pairs of groups. Results are presented in Table 6.5.

The U test showed a significant difference ($U = 118,5$; $p = 0,0308$; $r = 0,3381$) between the Follow-up and the Family planning groups, at a significance level of $\alpha = 0,05$. Other differences were found between the Family planning and the Infertility groups ($U = 46$; $p = 0,0041$; $r = 0,4845$). Considering the Post-partum and the Infertility pair comparison, the approximation to the form of the normal distribution is

Table 6.4: Percentage agreement with SDM-Q-9 contents from all Participants (General), and considering the purpose of the appointment with the Fertility*Care* instructor or medical advisor: Follow-up, Family planning, Post-partum follow-up and Infertility. Pregnancy follow-up was not considered due to the low number of answers, i.e. poor statistical significance. D - Disagree; A - Agree.

	General		**Follow-up**		**Family planning**		**Post-partum**		**Infertility**	
	D	**A**	D	A	D	A	D	A	D	A
I.	**10**	**90**	13	88	0	100	14	86	30	70
II.	**8**	**92**	13	88	0	100	14	86	20	80
III.	**12**	**88**	19	81	8	92	14	86	10	90
IV.	**10**	**90**	19	81	4	96	14	86	10	90
V.	**2**	**98**	0	100	0	100	14	86	0	100
VI.	**10**	**90**	19	81	0	100	14	86	20	80
VII.	**13**	**87**	13	88	4	96	14	86	40	60
VIII.	**12**	**88**	13	88	0	100	14	86	40	60
IX.	**8**	**92**	13	88	0	100	14	86	20	80

Table 6.5: Results of the Mann-Whitney U test performed in the six pairs of consultation purpose groups. z - z-score for the Mann-Whitney U test; p - probability; r - effect size.

Group pairs		**z**	**p**	**r**	significance at $\alpha = 0,05$
Follow-up	Family planning	2,1648	0,0308	0,3381	Yes
Follow-up	Post-partum	-1,4699	0,1416	0,3065	No
Follow-up	Infertility	0,6325	0,5287	0,1240	No
Family planning	Post-partum	-1,1168	0,2627	0,1974	No
Family planning	Infertility	2,8664	0,0041	0,4845	Yes
Post-partum	Infertility	-2,2934	0,0220	0,5562	Yes*

less robust, given that the sample size of the earlier group is less than 10. Nevertheless, the test showed a difference between groups ($U = 11$; $p = 0,0220$; $r = 0,5562$).

Perceptions of SDM considering if a decision was discussed

On the other hand, in Table 6.6 the average raw and transformed scores are presented considering the answers participants gave on whether or not a decision was discussed or revised. No major differences in SDM perception were registered, and the group that stated that *No* decision was considered scored a higher average TS, of $85,9$, from a range of $24,4$ to 100, than the group that responded *Yes*. From a range of 0 to 100, the *Yes* average TS was $82,7$.

Statistical analysis

An analysis was performed to compare the the TS between the *Yes* and *No* groups of participants. A Mann-Whitney U test ($U = 221$; $p = 0,2187$; $r = 0,1587$) indicated that one cannot conclude that a significant difference exists between the group that stated *No* ($median = 97,8$) decision was discussed or revised, and the group that stated *Yes* ($median = 87,8$) to the same question.

The same statistical test was performed taking into account the different items representing the different steps of SDM. Results were not presented given the fact that it was not possible to conclude that significant differences exist between the two groups being assessed. This results may appear because of the difference in the sample sizes. A total of 48 participants stated *Yes* to a decision being discussed or revised. Comparing with 12 answers from participants that perceived *No* decision was considered.

Table 6.6: SDM-Q-9 average Raw score (RS) and Transformed score (TS). Item-by-item average results from all Participants (General) and considering whether a decision was discussed in the last appointment.

	General	**Yes**	**No**
I.	**4,1**	4,0	4,8
II.	**4,2**	4,1	4,7
III.	**4,0**	4,0	4,0
IV.	**4,2**	4,2	4,2
V.	**4,7**	4,6	5,0
VI.	**4,1**	4,2	4,0
VII.	**4,0**	3,9	3,9
VIII.	**3,9**	3,9	3,9
IX.	**4,3**	4,3	4,2
RS	**37,5**	37,2	38,7
TS	**83,3**	82,7	85,9

6.3 Discussion

Shared decision-making is a concept that is becoming more present in today's health practice. The patients role in the decision-making process is not passive, as new demands are required. Access to different sources of information, good relation between doctor and patient, care provision and risk communication are indicators of patient engagement in healthcare [8].

Decision aids have been developed to support the decision-making process. With the CrM Fertility*Care* system, women and couples are equipped with the chart and information required to correctly observe and register the biomarkers to assess a woman's health and fertility. With that material support, in every follow-up session they attend, the method is revised and any doubts or concerns are discussed with the instructor or medical advisor.

In order to evaluate if the Fertility*Care* practice can be considered as a SDM approach, the 9-item shared decision-making questionnaire was considered [51]. The main purpose of the SDM-Q-9 questionnaire was to evaluate participants' perception of Shared decision-making. This in order to evaluate the CrM Fertility*Care* system as an approach to this practice.

Considering the different consultation purposes of the follow-up sessions and taking into account that decision-making is a process integrated by several steps, different perceptions were expected. The overall results present a high level of perception of SDM. But several differences were found when separating each step of the decision process, in the SDM-Q-9, and comparing the results between groups. The SDM-Q-9 survey has a clear uni-dimensional structure [59]. This can somehow obscure the complex process of shared decision-making, by giving the same importance to each one of its steps. This justifies the need to evaluate the questionnaire item-by-item. The questionnaire is theory-driven and describes SDM through key features and very practical steps seen as additive components rather than a collection of equivalent and items.

Taking in mind the appointment purposes gathered in the questionnaire, one can conclude that, regardless of the results obtained, the process of shared decision-making is distinct, depending on the reason of the follow-up session. This is a reflection of the different perspectives of the decision making

process in each setting. However, all groups emphasize the step where the Fertility*Care* instructor or medical advisor helps the individual understand the information. Given that in every follow-up session one of the moments is to support any doubts or concerns the woman or couple might have, and assess their understanding on the subject.

The Infertility group revealed the lowest TS of all groups. Namely in the steps of acquiescing that a decision is to be made, and the negotiation of the different options and decision making. Given the difficult situation, the waiting for the right diagnosis and the expectancy to achieve a pregnancy, one understand the results.

No significant differences were found when comparing the groups formed from the second question of the survey. It inquired the participants of whether or not a decision was discussed or reconsidered. Results showed no great difference in the TS's of the SDM-Q-9 among the groups, Table 6.6. Even the statistical test performed did not lead the conclusion that differences in perception were to be considered.

As a conclusion of the results, we can consider that Fertility*Care* can be perceived as a shared decision-making approach.

6.3.1 Limitations

Some limitations should be considered. The SDM-Q-9 is very practical and low-cost, it is not time consuming for the participants and is well accepted. However, self-report methods are subjective and have several limitations and so cannot truly capture the absolute level of SDM [59].

Another limitation is the representativeness of the data gathered. Only a limited number of participants responded to the questionnaire. A larger number of responses, during a larger period of time could have lead to a different set and amount of results. Data from Fertility*Care* does not yet have full digital support. This lead to some delays in sending out the online surveys, and the difficulty in gathering demographic information from the participants that took the questionnaire.

Chapter 7

Conclusion

This dissertation proposed to present Fertility*Care* as a SDM approach where patient engagement is the main focus. The concepts and basic frameworks of EBM and SDM are changing the grounds for the healthcare decision-making process. These new practices of healthcare should lead to better health outcomes and to a more effective use of healthcare resources [60]. And also the respect for patient autonomy and preferences.

Practical problems of implementation include training on communication skills, access to research and development of tools to share evidence and support the decision process. However, many research on how to adapt guidelines and tools to facilitate these approaches are being published [61].

FABM's use various biomarkers to identify days in the menstrual cycle to identify the most fertile period of the menstrual cycle. Being low cost, having no expected side effects and knowledge increase on reproductive physiology are among the advantages of using these methods [62].

The CrM Fertility*Care* system is set upon the standardized observation and reporting of vaginal discharge and bleeding. The recorded biomarkers can then be interpreted for fertility and health status. Women and couples are taught using a case management approach. Fertility*Care* practitioners and medical advisors provide the instruction and follow-up sessions.

7.1 Achievements

The follow-up consultations of the CrM Fertility*Care* system were the object under assessment in this dissertation.

A qualitative acknowledgement of whether or not Fertility*Care* respects the three pillars of Evidence-based medicine was developed. The best available evidence is supported by decades of research and scientific evidence developed on the matter [44]. Clinical expertise is assured by the training program and internship practice prior to being certified practitioners or medical advisors [63]. Finally patient preferences and expectations are the focus of the follow-up sessions, as well as their support on doubts and concerns on the methods or procedures.

Following that, the SDM-Q-9 was proposed to all former and present participants of Fertility*Care*,

in order to assess their perceptions of SDM concerning their last consultation with Fertility*Care*. Based on Makoul and Clayman's integrated model of SDM [52], the survey inquires participants to evaluate to which level they agree with each step of the decision making process. The scores of each item were summed up to get a RS, raging from $0 - 45$. That score was then resized to a TS, raging from $0 - 100$, for better understanding of results. The average SDM-Q-9 TS was of $83,3$. Results were then analysed considering the consultation purpose. General follow-up to revise the charting method, Family planning consultation either to avoid or achieve a pregnancy, appointments to assess the couples' Infertility, Post-partum follow-up, and pregnancy were the five groups considered. Visual representation of the TS obtained for each consultation purpose group are presented in Figure 7.1.

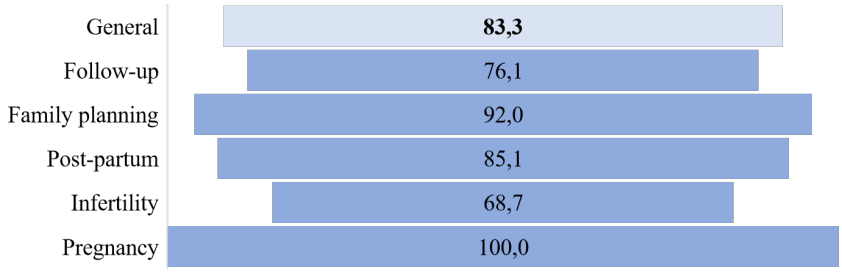

Figure 7.1: SDM-Q-9 average Transformed score (0-100) from all Participants (General), and considering the purpose of the last appointment with the Fertility*Care* instructor or medical advisor: Follow-up, Family planning, Post-partum follow-up, Infertility and Pregnancy follow-up.

Different perceptions regarding SDM, based on the consultation purpose of the participants, lead to different TS scores. The Infertility groups presented the lowest score. Those differences were analysed through a Kruskall-Wallis test, and to identify group-pair differences, Mann-Whitney tests were performed. Differences were identified between the Follow-up and Family planning groups ($U = 118,5$; $p = 0,0308$; $r = 0,3381$; $\alpha = 0,05$), between Family planning and Infertility groups ($U = 46$; $p = 0,0041$; $r = 0,4845$; $\alpha = 0,05$) and between Post-partum and Infertility groups ($U = 11$; $p = 0,0220$; $r = 0,5562$; $\alpha = 0,05$).

An analysis was also performed considering the participants answer to the question of whether or not a decision was discussed or revised. Even tough it was expected that the group whose answer was *No* decision was considered to score a lower TS, they happened to score a higher average TS, of $85,9$, from a range of $24,4 - 100$, than the group that responded *Yes*, with the average TS of $82,7$.

SDM-Q-9 as a self-report method is subjective and presents several limitations and so cannot truly capture the absolute level of Shared decision-making [59]. Another limitation was the reduced number of answers gathered from participants.

7.2 Future Work

The CrM Fertility*Care* system has great potential for improvement. The first step should be the development of better digital support platforms. One of the main difficulties of the present dissertation was the some data resources not being digitized.

There are known apps and platforms that provide a similar fertility awareness service, gathering the biomarkers information and recording them in an algorithm than can generate patters and predictions. The most noticeable example is FEMM^{TM} - Fertility Education & Medical Management. Their focus is to teach women to understand their bodies and vital signs patterns concerning their health. The support trough a free health app to help users track their health and reproductive goals. Diagnosis and treatment are supported on new research and medical protocols, and continuous research. And it offers training to individuals to become instructors of the FEMM health tracking to women and training to medical professionals in their methods and protocols [64].

A statistical appreciation of Fertility*Care* results on their areas of application, infertility, spontaneous recurring abortion, family planning and woman's health, could provide quantitative notice of their impact on women and couples that have participated in the program. For that I am more than willing to continue to collaborate.

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