Achieving optimal care for **women of childbearing age** living with chronic diseases

A POLICY REPORT

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[research, people, action]

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‘The lack of clinical evidence on pregnant women is a multi-stakeholder problem. The research community and industry are reluctant to develop trials in pregnant women due to concerns based on past tragedies; disease specialists do not think about their patients’ fertility goals; scientific journals do not ask if medicines were tested in pregnant women; and pregnant women are not organised in a way that enables them to make a change because pregnancy lasts only nine months.’

Rieke van der Graaf, PhD, Netherlands

Executive summary

After decades of clinical research focusing mostly on men, women seem finally to be similarly represented in clinical trials. However, one subgroup of women that remains largely excluded is pregnant women. As a result, evidence to drive clinical decisions in these women is often lacking. This has an impact not only on women who are currently pregnant but also those who may become pregnant – so-called 'women of childbearing age'.

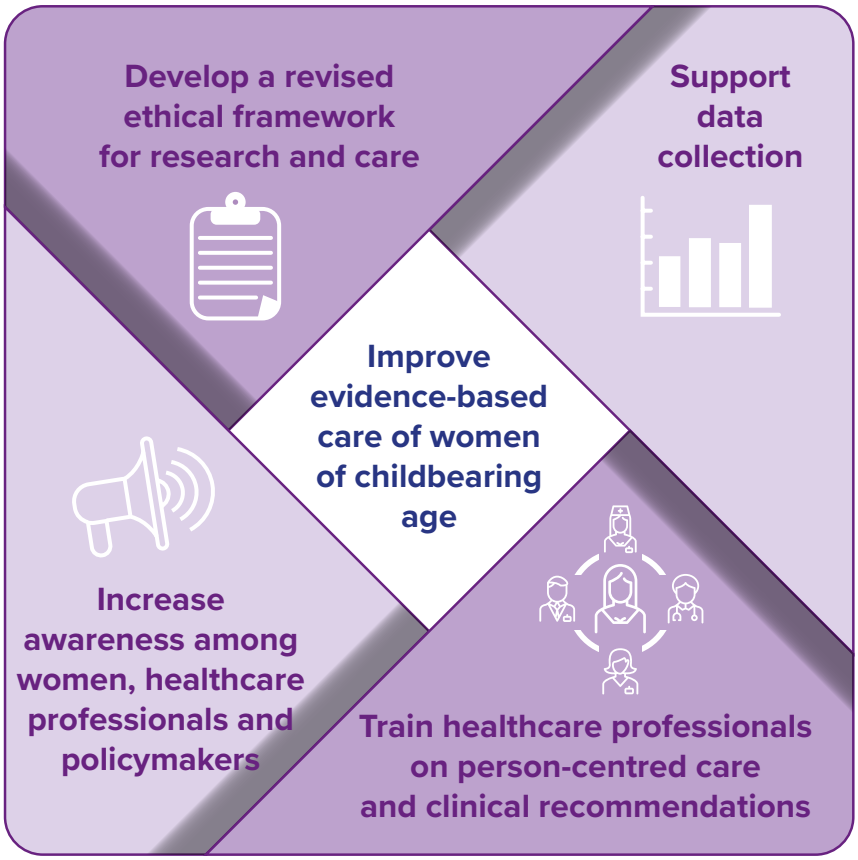
Treatment decisions in women of childbearing age are mostly driven by fears over what could happen to the unborn child. However, it is critical to recognise that leaving diseases untreated may in itself carry risks – to both the woman and the fetus.

No woman should have to choose between her health and having a child. Yet without suitable data to guide practice, we lack the understanding to offer optimal disease management in alignment with fertility goals to pregnant women, women who may face an unintended pregnancy and those who plan to conceive. Ethical frameworks governing decisions about whether to offer treatment to women of childbearing age need to be revised to consider both risks and benefits of each treatment option, including no treatment. This is a particular consideration for women living with chronic diseases because they may require ongoing medication, and treatment discontinuation before or during pregnancy may carry significant risks to their health.

There are several barriers to high-quality and evidence-based care of women of childbearing age living with chronic diseases. The traditional classification of pregnant women as a 'vulnerable' population has contributed to their low participation in clinical trials, perpetuating the cycle of limited data and evidence-based recommendations to drive practice. Women are often not involved in decision-making and their fertility goals are frequently not discussed throughout the management of their chronic diseases; this may itself be a result of other issues, such as insufficient training or awareness of existing evidence by healthcare professionals. Some of these issues are beginning to be addressed through regulatory advancements and the development of national and international research projects. However, we need to do more.

This report explores existing barriers to, and recent advancements in, care of women of childbearing age living with chronic conditions, with examples drawn from chronic inflammatory diseases, epilepsy and HIV/AIDS. We offer a set of recommendations for all stakeholders to ensure women of childbearing age receive care that aligns with their fertility goals. These recommendations have been developed around four pillars where action is needed most.

Pillars of action to improve care of women of childbearing age with chronic diseases



1 | Introduction

Medication is rarely tested in pregnant women, which leads to uncertainty in clinical practice when managing their health.[1-5] Without strong evidence, treatment decisions risk being based on anecdotal findings and fears over what could happen to the unborn child. This has an impact for all women who are pregnant or can potentially become pregnant, particularly those who live with chronic diseases that may require ongoing treatment.

No woman should have to choose between effectively managing her disease and having a child. In 2018, in the European Union alone, more than 2.7 million women were pregnant and over 4 million babies were born.[6] Data from Europe and North America suggest that a minimum of 44% of pregnant women take at least one medicine during pregnancy.[7 8] Excluding pregnant women – or those who may become pregnant – from clinical trial research means we are not collecting evidence to fully inform medication use in this significant population, denying them equal access to medical advances.[1 9]

This report aims to gain a better understanding of how we can progress to evidence-based, person-centred care for women of childbearing age, ensuring a balance between their health needs and fertility goals. It was developed based on a review of the literature, interviews with leading experts in the field, and case studies illustrating best practice in surmounting existing barriers. It focuses on women of childbearing age living with chronic diseases, with specific examples drawn from chronic inflammatory diseases, epilepsy and HIV/AIDS. It concludes with a set of recommendations for policymakers and the healthcare sector on how to create an enabling policy environment to support optimal care for women of childbearing age in years to come.

2 | Research in pregnant women: the policy context

The history of excluding pregnant women from clinical trial research

Until the early 1990s, clinical trial research focused largely on men.[10] As a result, efficacy and safety profiles of medicines were not fully understood in women – but women were still given these medicines.[11 12] In 1993, the US Food and Drug Administration (FDA) published guidelines to address gender differences in clinical evaluation of medicines,[13] and today men and women seem to be similarly represented in clinical trial research.[10] However, one subgroup remains largely excluded: pregnant women.

Concerns about conducting clinical trial research in pregnant women arise mostly from fear of fetal harm.[2 14] Many such concerns may result from the effects of thalidomide use in the late 1950s to manage morning sickness in pregnancy, which caused thousands of children to be born with severe birth defects, and an undetermined number of miscarriages and stillbirths.[15] This tragedy prompted a reluctance to give medicines to pregnant women.[1] However, thalidomide was not tested in pregnant women before being given as a treatment for morning sickness and, had relevant data been available, the tragedy could have been averted. Therefore, the key lesson from the thalidomide case should not be that pregnant women should be excluded from clinical trials, but rather that appropriate studies must be conducted to minimise the risks of teratogenesis (congenital malformations) and adverse events in pregnancy.[9]

> ‘When data are limited, pregnant women lose. They may be dosed incorrectly, or medicines can be withheld from them. Wrongful assumptions are made in the absence of data.’
>
> **Dr Anne Lyerly, US**

The ethical framework around clinical trial research in pregnant women

The exclusion of pregnant women from clinical trials is often justified on ethical grounds, yet this ethical basis may be misleading.[9 16] In the absence of reliable data on the effects of treatments in pregnant women, clinical decisions for these women sometimes end up being based on anecdotal findings and possibly ungrounded fears over what could happen to their babies. Yet it is important to recognise that not treating pregnant women also carries risks, as they remain exposed to the harmful effects of conditions they may have or contract. Thus, not treating them may in itself be considered unethical. These concerns apply not only to women who are currently pregnant but also those who may become pregnant – so-called 'women of childbearing age'. This term is typically used to denote all women between 18 and 45 years old.[14 17]

The ethical questions at play are most easily illustrated in the case of women who have chronic diseases requiring regular medication. For example, people living with diabetes have increased blood sugar levels (hyperglycaemia) and may need medication to manage symptoms and try to avoid additional health problems.[18 19] Studies suggest that poor glucose control before and during pregnancy is associated with an increased risk of congenital anomalies.[20] Therefore, pregnant women living with diabetes may not only require medication to control their symptoms but also to ensure normal fetal development. This shows the importance of considering risks and benefits for both the woman and fetus when managing chronic diseases during preconception and pregnancy.

The current policy landscape

The need to improve care of women of childbearing age with chronic diseases has not yet been a focal topic in some important health policies and plans across the world. The World Health Organization (WHO) 2016 strategy to improve women's health in Europe, for example, mentions the need for gender-responsive health systems but does not specifically discuss the challenges in management of chronic diseases in women of childbearing age.

However, there has been growing recognition of the need for evidence to support appropriate use of medication in pregnant women. In 2016, the US legislation 21st Century Cures Act[21] established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to help improve knowledge and research on safe and effective treatments in these populations.[22] In 2018, the FDA reversed its guidance excluding pregnant women from clinical trials.[7] In 2020, the European Medicines Agency (EMA) also recognised the need to promote the inclusion of pregnant women in clinical trials and detect medication safety issues in this population.[23] The new EMA guidelines on pharmacovigilance in pregnant and breastfeeding women, which were released for public consultation at the end of 2019, are expected to come into effect by 2021.[24] Several registries have been set up around the world to capture efficacy and safety data on the use of medicines in pregnant women.[25 26] Multi-sectoral initiatives have been established to reduce existing hurdles and barriers in regulatory, research and ethical frameworks, to ensure that all women who are, may become or wish to become pregnant have access to appropriate, evidence-based treatment.[27 28]

Despite these advances, many challenges remain in conducting clinical research in pregnant women and translating findings into appropriate, person-centred care for women of childbearing age.

3 | Key issues in improving care of women of childbearing age

> ‘There is a considerable lack of awareness of the challenges in clinical management of women of childbearing age concerning the safety of medications in pregnancy. The lack of evidence is not perceived as a problem, which hinders progress in the field.’
>
> **Professor Joan Morris, UK**

There are several issues that contribute to the challenges of treating women of childbearing age who have chronic diseases (*Figure 1*). These issues are intertwined and contribute to one another.

Figure 1. Key issues in improving care of women of childbearing age

3.1 | Lack of evidence to drive practice

The efficacy and safety of various medicines may be quite different in pregnant women compared with the rest of the population.[16 29 30] Women undergo complex hormonal and immunological changes during pregnancy,[31] and we lack a clear understanding of how different medicines may interact with these changes, or how these changes impact chronic diseases or medicines' activity.[16 29-32] For example, physiological changes during pregnancy may affect the concentration of a given medicine in a woman's bloodstream, thus impacting its effectiveness.[4 33]

Traditional exclusion of pregnant women from clinical trials has resulted in a limited evidence base to drive clinical decisions in a sizable population.[1-3 5] For example, in 2016, 44% of all adults living with HIV across the world were women of childbearing age, who need antiretroviral treatment to reduce the risk of transmitting HIV to their children.[34] There is a 15–45% risk of mother-to-child transmission of HIV during pregnancy, labour, delivery or breastfeeding[35] – a risk that can be reduced to less than 5% with antiretrovirals.[34] However, the possibility of an association between these medicines and adverse events in pregnancy is not fully known.[34 36] In fact, a recent study in Botswana[38] suggests one antiretroviral widely used in low and middle-income countries[37] may be associated with increased risk for neural tube defects. While more data are needed to validate findings, this is a good example of the importance of conducting clinical trial research and collecting and analysing data in pregnant women, so we can better understand the balance of risks and benefits associated with medication use in this population.[4]

> 'Many people, including healthcare providers, are unaware that most often medicines are used in a subpopulation that was not included in clinical trials. For example, medicines for rheumatic diseases are usually tested in women over 45, and many younger women receive those medicines.'
>
> **Dr Rebecca Fischer-Betz, Germany**

By failing to conduct clinical research in pregnant women, we are potentially depriving them of equal access to medical advances.[1 9] For example, the Swedish Reference Group for Antiviral Therapy recommends that recently approved antiretrovirals be avoided during pregnancy in favour of treatments that have been in use for longer, due to the greater uncertainty around adverse events.[33]

Lack of data often puts women and their physicians in the difficult position of having to balance family planning and treatment goals.[1] On one hand, women can take the medication that can help them manage the disease but may have unknown effects on the child. On the other hand, they can choose not to take medication, which reduces potential risks associated with the medication but can exacerbate their chronic disease, and this may itself harm the child or lead to adverse events in pregnancy.[39-41] This uncertainty often has a real impact on women's family planning decisions, as the fear of passing on health issues to the child frequently leads women with chronic diseases to delay having children or not have children at all.[42-44] For example, women living with psoriasis or rheumatoid arthritis are generally older at delivery than disease-free women,[45-49] and this difference is more evident with increasing severity of disease.[50]

> 'There is a need for awareness of the value of including pregnant women in clinical studies.'
>
> **Nele Caeyers, Belgium**

To compensate for the lack of randomised controlled trials, alternative methodologies are used to help increase understanding of the impact pharmacological treatments may have on pregnancy outcomes. These include registries, case reports, patient series and surveillance programmes from the pharmaceutical and biotechnology industry.[31] However, these methodologies have limitations and do not replace clinical trials. They may be subject to selection bias, because challenging cases are more likely to be included in case reports or patient series, for example.[31 51] They often have a limited sample size, lack control groups, may collect limited information per individual, and lose women and children to follow-up.[52] Speed of data collection in registries is also a limitation as it may take more than 20 years to collect enough evidence to understand the teratogenic potential of a new medicine.[53] In addition, registries for the same condition may collect different data, which reduces the ability to conduct statistical analyses and draw significant conclusions. Despite the potential limitations, registries are still the most valuable of these alternative methodologies for data collection, especially population-based registries,[9] such as those on pregnancy and psoriasis in Denmark and Sweden. By covering the national population, these registries limit selection bias and therefore allow for large studies that can consider multiple and rare outcomes.[46]

There have been several pioneering efforts to improve research and regulatory guidance around pregnancy.[54] Some of these are presented as case studies below.

Case studies

The Second Wave Initiative

The Second Wave Initiative was launched in the US in 2009.[27] It leads several projects in the identification of barriers to clinical research in pregnant women, for example by conducting ethical and legal analyses, and promotes the inclusion of pregnant women in research to increase evidence and improve care.[1] The Second Wave Initiative has been involved in the project Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES), which aims to develop 'ethically responsible, action-guiding recommendations for advancing research to address evidence gaps'.[55]

US Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

In the US there is a movement towards inclusion of all women in clinical research.[56] For example, in 2016, the 21st Century Cures Act established the multidisciplinary group PRGLAC to provide advice to the Secretary of Health and Human Services on gaps in knowledge and research on safe and effective treatment of pregnant and breastfeeding women.[57] The Task Force launched a report in September 2018 with 15 recommendations to improve research and support the development of evidence-based care in these populations.[22] PRGLAC is now working on providing guidance on the implementation of the recommendations.[58]

Dedicated pregnancy registries: EUROmediCAT and EUROCAT

The research consortium EUROmediCAT was developed in 2011 as a subsidiary project to the European Surveillance of Congenital Anomalies (EUROCAT) network to increase knowledge around medication use in the first trimester of pregnancy.[59] It uses data from EUROCAT registries and healthcare databases.[26 60] EUROmediCAT aims to develop a European reproductive pharmacovigilance system – looking specifically at the risks associated with new antiepileptics, insulin analogues, antiasthmatics and antidepressants – and a framework for evaluation of the efficacy of safety measures.[60] One of its challenges is that the data collected in different registries vary greatly and may not always be comparable, calling for elaborate standardisation techniques.[59]

In 2015, the German Rheumatism Research Centre Berlin (DRFZ) and the Rheumazentrum Rhein-Ruhr e.V. in Dusseldorf created Rhekiss, the German pregnancy register for inflammatory rheumatic diseases.[61] Rhekiss, in combination with national registries from Norway (RevNatus), France (EGR2) and Switzerland (RePreg), formed the European Network of Pregnancy Registers in Rheumatology (EuNeP) in 2017.[62] This collaborative initiative aims to combine data from the member registries to inform clinical practice and support the development of other national pregnancy registries, for example by creating a set of parameters that they should include.[25 61 63] In early 2019, EuNeP had information on almost 3,000 pregnancies, of which over 2,200 had been completed, in women living with rheumatic diseases in the four participating countries.[62]

ConcePTION: an international, comprehensive and collaborative research project

In 2017, the European public–private partnership Innovative Medicines Initiative launched a call for proposals on research in pregnant and breastfeeding women – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now (ConcePTION).[28] The five-year project was initiated in 2019 and aims to improve evidence on the use of medication by the populations under study, to disseminate findings and educate healthcare professionals to ensure they, and women, can make informed clinical decisions. ConcePTION includes eight work packages:

1. Commitment to move beyond pregnancy registries to generate evidence
2. Improvement of the collection, analysis and interpretation of pharmacovigilance data
3. Development of predictive preclinical models of breast milk concentration of medicines and exposure to breastfed infants
4. Development of a European breast milk research biobank and analytical centre
5. Dissemination and education
6. Cross-stakeholder engagement
7. Ethical, governance and quality assessment support
8. Scientific coordination, project management and sustainability.[64]

ConcePTION involves a collaboration of 88 institutions from 22 countries from the public and private sectors across Europe, including the EMA.[65] So far, over 2,700 women and healthcare professionals from 65 countries have contributed to the project's survey.[66]

Consolidation of teratology services: ENTIS and OTIS

Teratology services monitor and support the appropriate use of medicines during pregnancy and breastfeeding. National and local examples can be seen, for instance, in the UK,[67] the Netherlands[68] and Italy.[69] Examples of collaborative teratology initiatives include the European Network of Teratology Information Services (ENTIS) and the Organization of Teratology Information Specialists (OTIS).[70] [71] ENTIS is a multidisciplinary network established in 1990 that aims to prevent birth defects and developmental disorders that result from medication exposure in the womb or early in life.[72] It coordinates activities of different Teratology Information Services and collates and assesses data to support primary prevention of adverse events. OTIS is a professional scientific society established in 1987 in North America, aiming to connect experts in birth defects with the general public.[71] In 2002, it established a national call system to promote this connection, and in 2013 it launched the website MotherToBaby as a platform for public-facing services and research studies.

3.2 | Arguable classifications and unclear definitions

> ‘The “vulnerable” label puts pregnant women in a category where they don’t belong.’
>
> **Maxine Lancelot, Sweden**

Traditionally, the consideration of pregnant women as a ‘vulnerable’ group has limited their inclusion in clinical trials by not allowing them to be exposed to more than minimal risk, or making it easy to exclude them without justification.[2 9] Vulnerable populations are defined as those less able to protect themselves;[17] however, pregnant women are capable of giving consent or refusing study participation.[73] The traditional classification of pregnant women as ‘vulnerable’ partly results from the difficulty in distinguishing between the status of the woman and that of the fetus – the fact that the fetus could face harm without the ability to consent to this risk is given greater moral weight than the respect for a pregnant woman’s autonomy.[5] However, it is important to consider that the health of the fetus is linked to that of the woman, meaning that therapeutic benefits may also be linked, even if the distinction cannot be made.[2]

Some regulatory agencies and other relevant organisations have understood the need to abandon the ‘vulnerable’ classification of pregnant women. The revised US Common Rule,[74] which came into effect in January 2019,[75] does not include pregnant women as an example of a vulnerable population. In addition, the Council for International Organizations of Medical Sciences, which never classified pregnant women as ‘vulnerable’, now actively discourages the use of this term.[3 9] The American College of Obstetricians and Gynecologists has called for pregnant women to be classified as ‘scientifically complex’ rather than ‘vulnerable’.[73]

> ‘The choice of words plays a psychological role.’
>
> **Dr Rebecca Fischer-Betz, Germany**

It is also important to recognise that discussions around the lack of evidence to support clinical decisions in women focus predominantly on those who are pregnant or breastfeeding, but this evidence gap may impact any woman who can potentially become pregnant. When considering women of childbearing age, it is important to think about three groups: women who are already pregnant, those who may face an unintended pregnancy, and those planning to conceive. A sole focus on pregnant and breastfeeding women seems to disregard the possibility that almost any woman could become pregnant during her fertile years, and if she requires medication she may face major challenges in making appropriate clinical choices that protect her own health and that of any potential unborn child.

3.3 | Ethical frameworks overly focused on the risks of treatment

> 'We have a tendency to notice the harms of intervening and not notice the harms of not intervening. Risk trade-offs are part of life, part of pregnancy. We need to try to pull ourselves away from the presumption that we have the option of zero risk.'
>
> **Dr Anne Lyerly, US**

The ethical framework governing the administration of medicines to pregnant women has traditionally been driven by fears of possible risks to the fetus.[76 77] This disregards the fact that taking medication during pregnancy may also lead to clinical benefits to both woman and fetus, and that stopping treatment during pregnancy could, in fact, be a huge risk to their health. For example, abrupt discontinuation of treatment for epilepsy may result in epileptic seizures during pregnancy,[39] which can lead to adverse events and are linked to a tenfold increase in the risk of maternal death.[78] Stopping treatment in pregnant women living with axial spondyloarthritis, a rheumatic disease that affects the spine,[79] may also have negative consequences – it has been reported to increase the risks of a disease flare, and reinitiating treatment during pregnancy may not be enough to control symptoms.[80] In the case of women living with rheumatoid arthritis, while pregnancy often leads to alleviation of symptoms,[81-83] rheumatoid arthritis may increase the risk of adverse events in pregnancy – including the risk of preterm delivery and low birthweight[48 84 85] – which is especially relevant if the woman has not benefited from alleviation of symptoms and has high disease activity during pregnancy.[47 86]

In addition to being important during pregnancy, treatment may also be critical in the preconception phase. For example, in women living with rheumatoid arthritis, active disease in the months prior to conception increases the risk of flares during pregnancy.[87] Similarly, discontinuation of psoriasis treatment not only during pregnancy but also in the preconception phase may be impractical for many women and even unnecessary, as some medicines may not increase risks of adverse events or malformations.[31 88] These examples demonstrate the need to adequately manage chronic diseases before and during pregnancy to promote stable disease and minimal symptoms and risks.[41 80]

Fear of liability may be a disincentive for physicians to accept any risks associated with treatment in women of childbearing age.[77] Despite the need to consider both benefits and risks of taking medication, assessments are often biased towards risk – and this may be particularly true in women of childbearing age. For example, recommendations of treatment discontinuation are often based on limited evidence of safety rather than any evidence of harm.[89]

> ‘Some neurologists don’t feel confident managing epilepsy in pregnant women. Some even try to avoid contact with this population to avert legal consequences.’
>
> **Dr Manuel Toledo, Spain**

3.4 | Insufficient healthcare professional training

> 'Some rheumatologists frequently say "either pregnancy or treatment". But discontinuing treatment is not the only way for women living with rheumatic diseases to become pregnant.'
>
> **Dr Rebecca Fischer-Betz, Germany**

Even where data and guidance are available on the use of medicines in women of childbearing age, it can take a long time for evidence to be implemented in regular practice. Clinicians may not be aware of existing guidelines, or may not recognise the need for their implementation because of a lack of knowledge of the interactions between pregnancy, disease activity and medication.[77] Lack of training of healthcare professionals on the appropriate use of medication in women of childbearing age may be part of the issue. One notable example of the implementation gap has been seen for valproate. A widely used antiepileptic, valproate has been found to be associated with congenital malformations, and guidelines and recommendations around the world have restricted its use in women of childbearing age.[30 90-92] However, evidence shows that this information is not reaching all relevant physicians or women with epilepsy,[92] some of whom are still exposed to valproate while pregnant.[93] Similar situations have been seen with other medicines. For example, in France between 2007 and 2013, compliance with pregnancy testing in women living with psoriasis and taking acitretin, a known teratogen, was found to be low.[94] The medicine requires a three-year wash-out period before conception,[95] but pregnancy tests were performed in fewer than 15% of women starting treatment and rarely in the 24 months after stopping the medication.[94] Some regulatory bodies have recognised the importance of medicines' labels conveying information on prescription during pregnancy, and have updated their labelling requirements.[96 97]

Training of healthcare professionals on chronic disease management before and during pregnancy is vital, so they can understand when treatment should be maintained, adjusted or stopped. For example, women with epilepsy may need to continue receiving medication during pregnancy to prevent seizures, but their therapeutic regimen may need to be adjusted to ensure exposure to the lowest therapeutic dosage possible while maintaining clinical management and limiting adverse events in pregnancy.[98] However, not all neurologists adjust medication in these women,[99] increasing risks in their unborn children.

> 'It's important to train GPs. Epilepsy specialists only see the women with severe disease; the others are usually followed in primary care.'
>
> **Professor Sophie Dupont, France**

Lack of collaboration is also an issue, as chronic disease specialists and obstetricians may not work closely together in the management of chronic diseases during pregnancy. As a result, there is limited opportunity to develop consensus on the optimal treatment approach for their patients in view of fertility goals and overarching health needs, which may lead to conflicting clinical advice[41 100] and care not aligned with each woman's needs. Studies have pointed to more than half of women with a chronic inflammatory disease receiving inconsistent clinical advice from different healthcare professionals regarding their treatment options during pregnancy.[41 52 100] Women living with HIV have also described receiving variable advice from different healthcare professionals.[101] The fact that information on new medicines' labels seems to vary across countries may add to the confusion regarding potential risks and benefits.[102]

> 'The lack of cross-collaboration and communication among specialists is a barrier to coordinated care of women of childbearing age. It is a major obstacle in establishing optimal care for these women.'
>
> **Professor Monika Østensen, Norway**

Case studies

Training for chronic disease specialists on management of rheumatic diseases in women of childbearing age

The Spanish Society of Rheumatology has established a working group on rheumatic diseases in women of childbearing age, AFRODITA.[103] This group aims to train rheumatologists on monitoring and management of rheumatic diseases during pregnancy, and to develop a pregnancy registry for autoimmune and rheumatic diseases. It also seeks to improve knowledge around the impact of medicines used in rheumatology on fertility, pregnancy and breast milk production. Once a year, the group organises training courses for healthcare professionals on management of rheumatic diseases in women of childbearing age.[104] Each iteration of the course has around 60–70 participants, mostly rheumatologists but also nurses specialising in rheumatology. AFRODITA is seeking funds to establish the national pregnancy registry for rheumatic diseases.[104]

The Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases

The Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases provides support for management of rheumatic diseases in women of childbearing age across Norway, taking fertility goals into account.[105] The centre develops evidence-based guidelines and information leaflets to support both professionals and patients.[106] It provides courses for healthcare professionals and education sessions for women living with rheumatic diseases. This model works well in countries with a small population, while other countries may require a network of specialised centres working together to develop a national consensus and support all patients.

Updating the medicines labelling system

In 2015, the FDA changed the system of classification of risks for prescription medicines during pregnancy and breastfeeding, due to concerns that it was confusing and did not accurately communicate risk.[31] [107] The new labelling system,[96] the Pregnancy and Lactation Labeling Rule, requires a narrative for each medicine with detailed information across three categories: pregnancy, lactation, and females and males of reproductive potential. The narrative should include information about pregnancy registries. The implementation of this labelling system was planned to be gradual and completed by June 2020.[108] In Japan, the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency also improved labelling regulations.[97] A requirement for separate sections to convey precautions for women of childbearing age, pregnant women and breastfeeding women has been included in the country's Pharmaceutical Administration and Regulations guidance.[109] As for the EMA, it is unclear whether new labelling regulations will be implemented soon.

> 'Guidelines should be written with input from different healthcare professionals, otherwise gynaecologists and disease specialists have different protocols. We need unifying care recommendations across Europe that are easily accessible – this is worthwhile for both doctors and patients.'
>
> **Dr Manuel Toledo, Spain**

3.5 | Lack of a person-centred care approach regarding fertility goals

> ‘In recent years things have changed in Spain; many people want to be involved in their own care – they search for and find information online and want to discuss it with their physicians. Several doctors respond to this need and are involving women in their care. But, unfortunately, many others still don’t include them.’
>
> **Dr Juan Antonio Martínez Lopez, Spain**

Many women are not involved in clinical decisions that may have an impact on their fertility goals, or are left unsupported in making such decisions. Preconception counselling is essential, and is recommended in the management of chronic diseases in women of childbearing age.[30 110-112] However, a study of women living with a chronic inflammatory disease in Europe, the US and Japan reported that more than two thirds had to initiate pregnancy discussions themselves with their treating physician in clinical appointments before conception.[42] Empowering women to understand their situation and involving them in decisions regarding starting, discontinuing or changing treatment before and during pregnancy is key.

> ‘Women don’t know where to look for information on their chronic disease and fertility; they don’t know what to ask.’
>
> **Nele Caeyers, Belgium**

Poor communication about the potential effects of medication on fertility is a particular problem. For example, some antiepileptics reduce the effectiveness of several hormonal contraceptives, and combined hormonal contraceptives may reduce the effectiveness of some antiepileptics.[113] This calls for therapeutic adjustments to ensure effective and safe treatment while reducing the risks of an unintended or complicated pregnancy. However, many physicians do not consider this issue or communicate it to their female patients.[99] This is not exclusive to women living with epilepsy. More than a third of women with chronic inflammatory diseases have reported feeling that they lack information on the impact of treatment decisions on pregnancy, or that their concerns are not adequately addressed in medical appointments.[41 42] In many disease areas, patient organisations may help to fill this gap by providing women with information to help guide their decisions regarding treatment and fertility.

> ‘Some neurologists don’t know that women with epilepsy have more difficulty in becoming pregnant than the general population. It is important to discuss this association early on and refer female patients to fertility specialists if needed, and certainly before women have spent years trying to become pregnant.’
>
> **Dr Manuel Toledo, Spain**

Joint consideration between women and their physicians of treatment and fertility goals is particularly important to avoid unsupervised treatment discontinuation. Public perception that virtually all medication taken during pregnancy could negatively impact fetal development may lead to a high risk of treatment discontinuation by women during preconception and pregnancy, sometimes without consulting a healthcare professional.[42] This may increase risks for both the woman and child. Women with epilepsy often stop their medication when they become pregnant because they are not warned of the risks of treatment discontinuation.[99] Women with rheumatoid arthritis also seem prone to discontinuing their medication during pregnancy, particularly in the first trimester.[114] It is therefore crucial to discuss these risks over the course of the management of chronic diseases in women of childbearing age.

> ‘In family planning you have to explain why there is a lack of evidence and how we can interpret the limited data available. It’s a special type of communication, so training is needed in shared decision-making.’
>
> **Dr Rebecca Fischer-Betz, Germany**

Case studies

Patient associations providing information online

Several patient associations provide information on their websites regarding chronic diseases and pregnancy. The National Psoriasis Association in the US, for example, provides extensive information online on pregnancy and breastfeeding in women living with psoriatic disease.[115] [116] The website of the National Ankylosing Spondylitis Society in the UK highlights the importance of women living with ankylosing spondylitis being able to discuss pregnancy with their rheumatology team.[117] It provides information on the potential interaction between medicines and pregnancy outcomes, and includes direct links to clinical guidelines.

Patient associations empowering women via short courses and events

Some patient organisations have focused on empowering women of childbearing age with chronic diseases through direct interaction to enable them to understand and participate in clinical decision-making. ReumaNet – a network of patient organisations in Flanders, Belgium focused on rheumatic diseases – organises an educational and support programme every two years for expectant parents and young mothers.[118] Participants have sessions with different specialists (rheumatologist, gynaecologist and psychologist) and one focused on self-management.[119] Following a 2014 report from the European League Against Rheumatism which identified concerns regarding sexual health, including pregnancy, in young people with rheumatic and musculoskeletal diseases,[120] the Dutch patient association Youth-R-Well.com organised an event to address these concerns.[121] The event provided an informal environment where participants could ask questions to three speakers; a rheumatologist, a sexologist and a young woman living with a chronic disease who had experienced pregnancy herself. The event was well-received, and participants scored highly the opportunity to speak with a rheumatologist in such an environment.

4 | Key recommendations to improve care

As evidenced in the previous chapters, we are a long way away from providing evidence-based care to women of childbearing age with chronic diseases. We believe there are four main pillars of action required to change this (*Figure 2*). Within each pillar, we have identified specific actions to improve care (*Figure 3*), which are discussed further in this chapter.

Figure 2. Pillars of action to improve care of women of childbearing age with chronic diseases

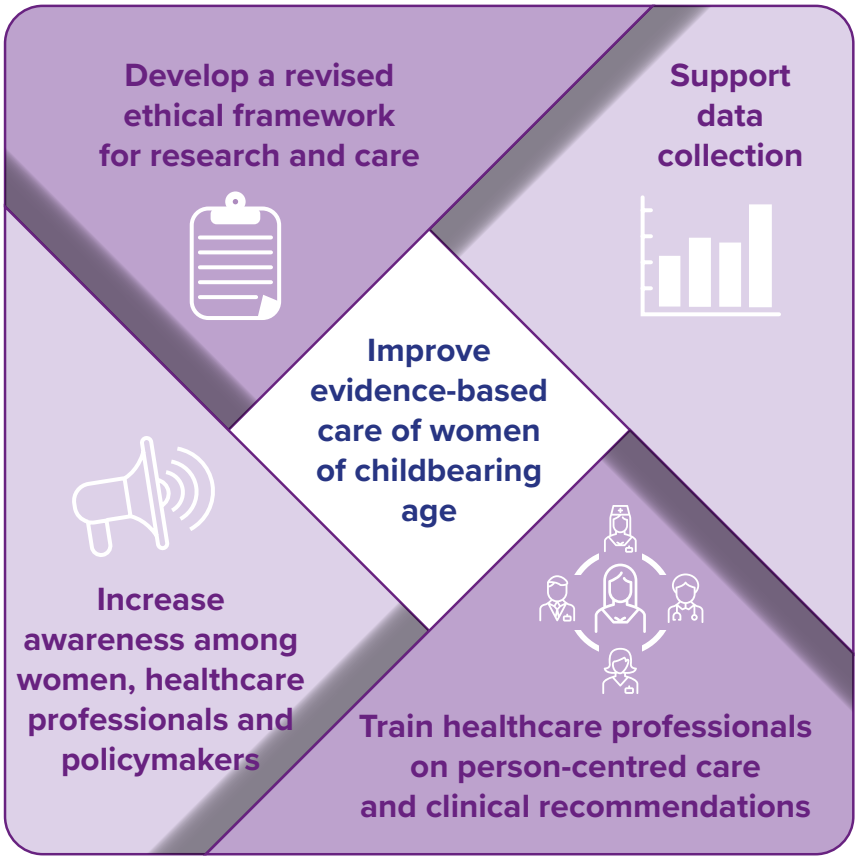


Figure 3. Key actions to improve care of women of childbearing age with chronic diseases

Develop a revised ethical framework for research and care

- Regulatory bodies should classify pregnant women as a complex, rather than vulnerable, population
- The healthcare sector should accept that not providing treatment may carry risks, and should ensure a proper assessment of benefits and risks of all treatment options

Support data collection

- The research community should develop a clear pregnancy research agenda
- Research methodologies and collaboration across the research community should be optimised to improve data collection
- Teratology services should be kept up to date to help avert birth defects

Train healthcare professionals on person-centred care and clinical recommendations

- Professional societies should work together on joint clinical guidelines advocating a person-centred care approach, including discussions of fertility goals
- Pharmaceutical companies, professional societies and patient advocacy groups should actively disseminate findings and recommendations to inform clinical practice
- Continuing professional education should be provided to all healthcare professionals to improve preconception counselling

Increase awareness of these issues among women, healthcare professionals and policymakers

- Multi-funded public awareness campaigns should be developed to shift mindsets among the general public
- Healthcare professionals should work with patient organisations and women's groups to empower women to participate in discussions about aligning their care with fertility goals
- Cross-sectoral, multidisciplinary initiatives should be established and should include women and women's groups

Pillar 1

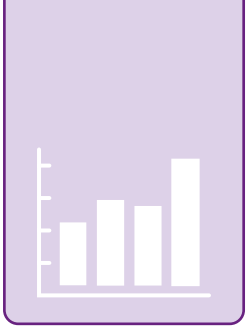
Develop a revised ethical framework for research and care

Regulatory bodies should classify pregnant women as a complex, rather than vulnerable, population

Experts have argued against classifying pregnant women as vulnerable, suggesting they are instead classified as a complex population.[2 9 17 73] Pregnant women are able to make their own decisions and refuse clinical trial participation; therefore, as a population group, they do not fall under the definition of vulnerable. Classifying them as complex would facilitate their inclusion in clinical trials while acknowledging that they would require special scientific and ethical considerations.

The healthcare sector should accept that not providing treatment may carry risks, and should ensure a proper assessment of benefits and risks of all treatment options

It is important to recognise that there is a tendency to consider only the risks of intervention and to overlook associated benefits – a bias towards negative outcome as a result of action not taken instead of action taken.[77] A cultural shift is needed to adopt a more balanced assessment – recognising that risks and benefits are part of taking any medicine. Regulatory guidance and ethical frameworks are needed to guide clinical research in women of childbearing age and mitigate liability for research institutes as well as medicines manufacturers.[4] Strategies can include targeted incentive programmes or official requirements of data collection.[22] Clear ethical frameworks are also needed to guide daily clinical practice to support women to continue taking medication during preconception and pregnancy, and ensure medical recommendations are based on robust scientific findings.



Pillar 2

Support data collection

The research community should develop a clear pregnancy research agenda

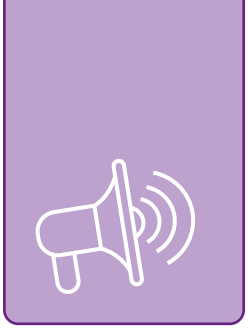
It is vital to develop a research agenda focused on improving care of women with chronic diseases and aligning that care with fertility goals, both in the preconception phase and during pregnancy. This agenda should identify questions that can already be addressed with existing data, propose new and relevant studies, and promote evidence-based clinical practice.[2 4] It should be developed jointly by those involved in research in both public and private settings, from academia to public–private partnerships and industry.

Research methodologies and collaboration across the research community should be optimised to improve data collection

High-quality management of chronic diseases in women of childbearing age requires a greater understanding of the natural evolution of each disease during pregnancy, and of the safety profile of different medicines when used in pregnancy. There is a need for studies with clear methodologies; research should be prospective, preferably start when a pregnancy is planned, include comparator groups and ensure high follow-up rates.[89] Comprehensive pregnancy registries can identify associations of interventions with adverse events in pregnancy, congenital malformations and developmental disorders,[51 122] but their methodologies should be improved to ensure they reach their full potential and produce comparable data. Multi-stakeholder and international collaboration is also needed to ensure optimisation of data collection methodologies.[2 89]

Teratology services should be kept up to date to help avert birth defects

It is important to keep teratology services up to date to reduce the negative impact of medication use during pregnancy. The potential of these services can be increased through networks that combine data collected in different regions or countries.



Pillar 3

Train healthcare professionals on person-centred care and clinical recommendations

Professional societies should work together on joint clinical guidelines advocating a person-centred care approach, including discussions of fertility goals

Chronic disease guidelines should include maternity and fertility expertise to support women to achieve their fertility goals. Clinical practice recommendations may play a key role in connecting healthcare professionals who would typically discuss women's fertility goals (fertility experts, gynaecologists and obstetricians) with those managing chronic diseases. Ideally, guidelines should be uniform across countries. They should elaborate on the need for clear communication and shared decision-making between healthcare professionals and women with a chronic disease.

Pharmaceutical companies, professional societies and patient advocacy groups should actively disseminate findings and recommendations to inform clinical practice

It is crucial to make publicly available the findings of pharmaceutical companies and research institutions so that they can reach the widest possible range of healthcare professionals and women with chronic diseases.[41 89] Professional societies and patient associations should have an active role in the dissemination of clinical findings and recommendations in available guidelines.

Continuing professional education should be provided to all healthcare professionals to improve preconception counselling

Ideally, healthcare professionals should discuss family planning with women throughout management of a chronic disease, even before the woman becomes pregnant.[32 111 117 123 124] They should actively try to understand the fertility goals of each woman, making sure her wishes are considered in clinical recommendations. This may play a vital role in empowering women to make decisions that meet their personal goals. Doctors should explain risks and benefits in order to prevent treatment discontinuation without medical supervision,[42] and they should encourage open communication between the woman and her care team.[22] Training in communication skills is key; for example, assessment of preconception counselling practice should be part of clinical training and performance evaluation.[90]

Pillar 4

Increase awareness of these issues among women, healthcare professionals and policymakers

Multi-funded public awareness campaigns should be developed to shift mindsets among the general public

Carefully crafted awareness campaigns are needed to address misconceptions about treatment in pregnant women. Clear and evidence-based information needs to be conveyed to healthcare professionals, policymakers and the general public about the lack of (and need for) clinical trial evidence, the challenges in clinical management of chronic conditions in women of childbearing age, and the risks of active disease during pregnancy.[22]

Healthcare professionals should work with patient organisations and women's groups to empower women to participate in discussions about aligning their care with fertility goals

Women need to be empowered to make informed decisions that meet their health and family planning goals. Close collaboration between healthcare professionals, patient associations and women's groups may help achieve this. Better information should aim to improve women's understanding of the lack of evidence but also of the possibility of fulfilling pregnancy goals even if they have a chronic disease.

Cross-sectoral, multidisciplinary initiatives should be established and should include women and women's groups

Multi-stakeholder collaborations focused on clinical management of women of childbearing age should always involve women and women's groups to be sure to accurately represent their views in any recommended actions.[4] For example, while it is sometimes believed that pregnant women would not want to join clinical research studies, experts who work closely with pregnant women report otherwise; some women wish to be part of clinical trials to help others and to ensure they themselves are closely monitored.[43]

5 | Conclusions

Management of chronic diseases in women of childbearing age is suboptimal due to insufficient evidence and decision-making based on fears of fetal harm that might result from treatment. There is an ongoing lack of research, which is compounded by a lack of clarity at the regulatory level. In addition, many healthcare professionals lack evidence on the use of medicines during preconception and pregnancy. This creates a cycle of clinical decisions being based largely on precaution and anecdotal evidence, often resulting in care that is not aligned with each woman's fertility goals.

The time has come to break this cycle. The complexity of the issue will require all stakeholders to work together – to shift mindsets, revise ethical frameworks and create innovative partnerships to collect evidence to guide clinical care.

This issue is critical – not just for women, but for society in general. Every year, millions of women become pregnant, and inevitably many of them will have a chronic disease. Current research, regulation and practice may be putting many women in the unfair position of having to choose between managing their disease and having a child. This is unacceptable. It is our hope that the actions set forth in this report may help rectify this situation.

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