Does women's health matter, and is clinical development failing them?

Historically, women have largely been left out of clinical research. How has this harmed women-specific healthcare, and what can be done to ensure this doesn't happen in the future?

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What do we mean by 'women's health'? There are many different aspects, but perhaps most crucially, and controversially, is whether we mean 'women' by sex or by gender. Both have an impact on health and health outcomes, and both are huge topics in their own right. This article will focus on the impact of sex (the biological/genetic characteristic) rather than gender.

The topic of women's health has been gaining traction and attention on social media, and multiple reviews and reports show that women feel ignored by or excluded from healthcare and clinical development.[1] But is this actually the case, and if so – does it matter?

Is there a bias? Is it real?

Although women, on average, live longer than men, they spend a greater proportion of their life in poor health.[2,3] In recent years, underfunding and lack of research in areas of female-specific health has been identified and highlighted.[4] The publicity has resulted in some health concerns specific to those born female such as endometriosis, polycystitis and menopause receiving more publicity and funding.

There has also been a significant societal shift in many countries (although not all), removing some of the stigma and reticence in discussing women's health, which has enabled women to be more proactive in seeking healthcare and support.

However, women's health is not confined to their reproductive organs and, welcome as the funding and awareness for these concerns is, much of the female population has been marginalised from healthcare in general, and from drug development in particular. This was highlighted recently in the press with a longevity study conducted solely on male mice. The authors stated that 'a drug that had been tested only on male mice was "vanishingly unlikely" to work on females'.[5] Yet, despite this difference being well known, there have been no studies aimed at female longevity.

The fundamentals of medicine assume that men and women present with conditions in the same way. Increasingly, this is being found to be incorrect, but still the presentation by women is referred to as 'atypicial', and rather than describing the male and female as two different sets of presentations, the male presentation is considered representative of the norm. In addition to presenting with conditions differently, women also respond to medicines differently. Sex is likely to affect pharmacokinetics, pharmacodynamics and safety profiles to some degree. It has been estimated that 50-75% of interindividual variability can be accounted for by sex differences.[6] And yet, even *in vitro* and non-clinical studies underrepresent women, and clinical research studies are predominantly designed with male patients in mind.[7,8]

This was exemplified by studies on low methionine diets, which reported that the diet extended life by over 40% in rats. This finding was confirmed by several follow-up studies. However, the rats in every study had been exclusively male, and when the studies were repeated with female rats 12 years later, the diet caused a number of the female rats to die prematurely.[9]

Non-clinical testing of pharmaceuticals is a crucial part of clinical development. However, non-clinical studies are generally skewed towards more male than female animals, even for those conditions that disproportionately affect women: a survey of 2,000 animal studies found that 80% had a male bias.[10] Since the cellular pathways underlying conditions may be affected by sex, this failure could result in a missed opportunity to identify any sex-related differences.

The impact of this means that, even before pharmaceutical products progress to phase 1 studies, several opportunities to identify potential differences in the way sex plays a role in patients' responses to treatment are likely to have been missed. The inclusion of both genetically male and female cells could identify sex differences early in the development life cycle.[11] Both genetically male and female animals should also be used for the next phase of studies. This is because differences between male and female subjects are found beyond the reproductive system, which means that sex should be considered an important biological variable in biomedical research.[12]

What are the causes of this bias?

Many of the attitudinal problems can be traced back to discriminatory views on women being 'feeble', 'feeble-minded', 'the weaker sex' and generally a small, below-par man with some reproductive organs. Experimental variability in animal studies is often cited as a reason for single-sex studies, although this is no longer believed to be the case.[13,14] In clinical studies, women were initially excluded due to safety concerns following the thalidomide tragedy, and in fact the US Food and Drug Administration (FDA) did not recommend testing drugs on women until 1993.[15] However, despite the recommendation to include women now being in place, insufficient inclusion of women at all stages of clinical development is still present. Phase 1 trials, which historically were male only, had only approximately 22% female inclusion in 2018.[16] This means that critical results for pharmacokinetics, pharmacodynamics and adverse drug reactions – on which a whole development programme is based – are still formed almost solely on data from men.

International guidelines (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH]) recommend that women be included in clinical trials in proportion to their prevalence in specific health conditions, however these are guidelines – not regulations – and are rarely enforced by the regulatory agencies. In 2019, 16 out of 40 medicines registered by the FDA for conditions affecting both men and women had a female study population of 50% or less.[17] This can lead to gaps in prescribing information, or assumptions that are not true for women.

This was illustrated by the development of emtrictabine/tenofovir for pre-exposure prophylaxis, which was approved in the US only for men with male sex assigned at birth and transgender women. Difficulties in enrolment, resource limitations and equivocal expectations of reaching meaningful clinical outcomes were cited as reasons to exclude women. Therefore, 'difficult enrolment' meant that 51% of the population were immediately excluded from both the study, and eventually from the treatment, due to their sex.[18] However, these reasons are not universally applied; the FDA specifically states that low accrual rates for men in breast cancer trials is not an acceptable reason for their exclusion from studies.[19]

The incidence of a disease should not be the sole basis for the inclusion of women. Women present, progress and have different outcomes compared with men for many progressive diseases, including Alzheimer's disease, cardiovascular

disease, depression, lung cancer, multiple sclerosis, obesity, osteoporosis and thyroid disorders.[20] Therefore, their inclusion in all stages of clinical research is key.

How are the data used?

Once the 'hurdle' of including women in clinical trials has been overcome, there is the question of what to do with any data generated. Only around 20% of registered COVID-19 trials analysed by Brady et al included some form of sex-specific analysis.[21] Any sex-specific analyses that were included were varied, but included the use of sex in forest plots and sex disaggregated efficacy and safety data. In 2021, Schreuder et al reported that there had been little if no progress in the reporting of sex-specific outcomes in clinical trials for cardiovascular disease between 2010 and 2017, and sex-specific efficacy endpoints were reported in only 34.5% of the main publications of trials from 2010 and 23.5% of trials in 2017. Sex-specific safety outcomes were reported even less frequently: in only 11.1% and 8.6% of trials in 2010 and 2017, respectively.[22]

To overcome potential issues associated with the recruitment of women into clinical trials, sex differences are often studied as a subgroup. However, studies are rarely powered to enable appropriate detection of subgroup differences, and so any found are rarely included in the advice given to prescribers. This means that the data rarely leave the confines of the clinical study report, and this has serious consequences. Studies indicate that women report a higher incidence of non-serious adverse drug reactions (ADRs) than men, whilst men have a higher incidence of fatal and serious ADRs.[23,24] In 2013, the FDA halved the recommended dose of zolpidem for women because they metabolise the drug differently from men – concentrations in women the day after a dose has been taken were found to be high enough to potentially impair driving and other activities that require full alertness.[25]

Other impacts

If not for moral and ethical reasons, greater inclusion of women in clinical development is important for economic reasons. Between 1997 and 2000, eight prescription drugs were retracted from the US market because inadequate clinical testing in women had failed to identify that the drugs put women at greater risk of developing health problems than men. This error cost pharmaceutical companies and taxpayers an estimated $1.6bn per drug.[8]

The main guidance followed by companies seeking to develop novel therapeutics is published by the regulatory agencies (eg, the FDA or EU European Medicines Agency [EMA]) or by the ICH. However, guidance from all these agencies often conflate the terms sex and gender, refer to sex-related differences rather than

factors, and do not provide clear instructions on the use of sex-disaggregated data throughout the development life cycle.

The future

Things are starting to change. Both the FDA and EMA are starting to amend language to be more precise in their terminology. The FDA has developed diversity and inclusion documentation – Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry – which, coupled with the action plan to enhance demographic subgroup data (FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data) is attempting to improve the collection of a variety of data, including that relating to sex. The 2024 FDA Diversity Action Plan, when finalised, will require sponsors to specify and give rationale for their diversity goals and explain how they intend to meet them, with sex being a key demographic characteristic of the guideline.

The EMA Clinical Trials Regulation No 536/2014 requires participation of both sexes in clinical trials – representative of the target population – with sex-disaggregated data. Health Canada is making a concerted effort to increase the availability of sex-specific data in their 2021 *Sex- and Gender-Based Analysis in Action* paper. The Guidance Document: *Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences* – first published in 1997 and updated in 2013 – calls for sex-disaggregated data and inclusion of both sexes in research. Its Disaggregated Data Questionnaire has the stated aim to 'have all clinical evidence disaggregated by subpopulations, especially in pivotal clinical trials'.[26]

In 2016, the National Institutes of Health (NIH) enforced a requirement for the inclusion of male and female samples, and in 2022 the UK government published the Women's Health Strategy for England, which recommended that non-clinical studies use both male and female animals.[27,1]

The ICH has not updated its documentation and has stated that, as sex/gender is already mentioned in existing guidelines, sex specific guidelines are not required. It is hoped that this stance may be re-assessed soon.

The topic is gaining traction and publicity. In the same way that our thinking and attitudes evolved in paediatrics from considering and prescribing for children as 'small adults', the Beyond Bikini Medicine campaign launched by Women in Pharma aims to highlight that women, aside from those parts covered by a bikini, are not just 'small men'.[28]

There is still a long way to go. A 2020 paper replicating the study conducted by Zucker and Beery in 2009 found that, although the number of sex-inclusive research studies increased across most biological disciplines, approximately one-third failed to report the sample size by sex, and there was no improvement in sex-based analyses.[29] With an increasing public outcry about the bias in clinical development, the hope is that this can and will be addressed in the future.

It matters

It is clear that the bias is real, and the gaps in our knowledge related to the impact of sex on the outcomes of treatments are stark. As described above, the regulatory agencies are starting to update their documentation to prevent conflation of terms, which is the first step in providing clear guidance on what should be collected. In addition, an increased spotlight on women's health and historical underreporting of data will further push agencies and drug developers to look more closely at both the design of their studies (non-clinical and clinical) and how they report and publish the results. Sex and gender equity in research (SAGER) is an international set of guidelines (or 12 'rules') that aims to encourage reporting of sex and gender in a systematic way, across scientific disciplines.[30] The adoption and implementation of SAGER by journals will influence the public reporting of results.[31]

All these initiatives will give a clearer picture of the safety and efficacy of treatments at all stages of development, and perhaps improve the safety of treatments. Surely this can only be a good thing for all involved, both men and women.

References:

1. *Visit: gov.uk/government/publications/womens-health-strategy-for-england*
2. *Patwardhan V et al (2024), 'Differences across the lifespan between females and males in the top 20 causes of disease burden globally: a systematic analysis of the Global Burden of Disease Study 2021', The Lancet Public Health 9(5): e282-e294*
3. *Visit: eige.europa.eu/publications-resources/toolkits-guides/*

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gender-equality-index-2019-report/women-live-longer-poorer-health

4. Smith K (2023), 'The funding gender gap', Nature 617, pp28-29
5. Visit: theguardian.com/science/article/2024/jul/22/sex-bias-labs-women-losers-research-ageing
6. Spear BB et al (2001), 'Clinical application of pharmacogenetics', Trends Mol Med 7, pp201-204
7. Franconi F et al (2014), 'Pharmacogenomics, pharmacokinetics and pharmacodynamics: interaction with biological differences between men and women', Br J Pharmacol 171(3), pp580-94
8. Haupt S et al (2024), 'Neglecting sex and gender in research is a public-health risk', Nature 629, pp527-30
9. Liu Y et al (2024), 'Methionine restriction diets: Unravelling biological mechanisms and enhancing brain health', Trends in Food Science & Technology 149:104532
10. Zucker I et al (2010), 'Males still dominate animal studies', Nature 465, pp690-690
11. Tannenbaum C et al (2017), 'Age and sex in drug development and testing for adults', Pharmacol Res 121, pp83-93
12. Lee S K (2018), 'Sex as an important biological variable in biomedical research', BMB Rep 51, pp167-173
13. Graham B M, 'Battle of the sexes: who is more variable, and does it really matter?', Nature 52, pp107-108
14. Beery A K (2018), 'Inclusion of females does not increase variability in rodent research studies', Current Opinion in Behavioral Sciences 23, pp143-149
15. Visit: fda.gov/media/71107/download
16. Labots G et al (2018), 'Gender differences in clinical registration trials: is there a real problem?', Br J Clin Pharmacol 84(4), pp700-707
17. Ravindran T S et al (2020), 'Making pharmaceutical research and regulation work for women', BMJ 27, 371:m3808
18. Goldstein R H et al (2019), 'Gender Parity in Clinical PrEP Trials', Reply, N Engl J Med 26, 381(26), pp2585-2586
19. Visit: fda.gov/regulatory-information/search-fda-guidance-documents/male-breast-cancer-developing-drugs-treatment
20. Yoon D Y et al (2014), 'Sex bias exists in basic science and translational surgical research', Surgery 156(3), pp508–516
21. Brady E et al (2021), 'Lack of consideration of sex and gender in COVID-19 clinical studies', Nat Commun 6, 12(1), 4015
22. Schreuder M M et al (2021), 'Reporting of sex-specific outcomes in trials of interventions for cardiovascular disease: Has there been progress?', Maturitas 144, pp1-3
23. Holm L et al (2017), 'Influence of age, sex and seriousness on reporting of adverse drug reactions in Sweden', Pharmacoepidemiol Drug Saf 26(3), pp335-343
24. Shepherd G et al (2012), 'Adverse drug reaction deaths reported in United States vital statistics, 1999-2006', Ann Pharmacother 46(2), pp169-75
25. Visit: fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-new-label-changes-and-dosing-zolpidem-products-and
26. Visit: canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/disaggregated-data-questionnaire-submissions.html
27. Visit: grants.nih.gov/grants/guide/notice-files/not-od-15-102.html
28. Visit: womeninpharma.network/campaign/beyond-bikini-medicine
29. Woitowich et al (2020), 'A 10-year follow-up study of sex inclusion in the biological sciences', eLife 9, e56344
30. Franconi F et al (2019), 'Sex-Gender Variable: Methodological Recommendations for Increasing Scientific Value of Clinical Studies', Cells 8(5), p476
31. Visit: doi.org/10.1186/s41073-016-0007-6

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