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Pregnancy in the time of COVID-19: what are the challenges for maternity care?

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Pregnancy is a period of profound physiological and psychosocial adaptation. The onset of the COVID-19 pandemic in early 2020 presented unique challenges for the maternity sector globally. Pregnant women are known to be more vulnerable to severe complications from respiratory infections due to physiological changes in their immune, cardiorespiratory and haematological systems. Our immediate concern in 2020 was for the safety of pregnant women and preventing the high rates of morbidity and mortality seen previously with the Middle Eastern Respiratory Syndrome and SARS CoV-1 epidemics.

Our fears for maternal health were compounded by uncertainty around mother-to-child transmission of SARS-CoV2 and the impact of SARS-CoV2 on fetal development, obstetric outcomes, and newborn health. There were also the potential adverse effects of medical interventions for critically-ill pregnant woman that had to be weighed up in clinical decision making.

While there was rapid progress in establishing trials to develop therapies and vaccines for COVID-19, pregnant women were arbitrarily excluded from many of these early studies, thus limiting the evidence base for clinical care. Vaccine hesitancy was therefore more pronounced among pregnant women in many countries.

And last, though not least, hospital visitor restrictions, the perception of hospitals as hot spots of infection, social distancing, reduced in-person care and, in some countries, routine separation from the baby after delivery, created great psychosocial stresses for mothers and their families.

In this Q&A article, global experts in perinatal epidemiology, maternal fetal medicine, maternal and child health, and vaccine uptake discuss the challenges in caring for pregnant women and their newborns during the pandemic and the progress that has been made.

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What can you tell us about the impact of SARS-CoV2 infection in pregnant women?

Marian Knight: This is actually a far harder question to answer than it might immediately appear, primarily because of differences in thresholds for testing, admitting and treating pregnant women. My answer has changed through the course of the pandemic, as different variants and differential treatment have changed the relative impact on pregnant women. Currently, it is clear that the Delta variant, coupled with very low levels of vaccination in pregnancy, means that SARS-CoV-2 is having a disproportionate effect on pregnant women compared with the non-pregnant population. Pregnant women are disproportionately represented amongst women of reproductive age admitted to intensive care with COVID-19, and, in the UK at least, maternal mortality is higher in the Delta wave of infection compared with previous waves (Alpha and wild type). The underlying reasons for this disproportionate effect are several, and include not only the low vaccination rates, but the fact that virus is now circulating at much higher levels in younger population groups with less social distancing and pregnant women are therefore more likely to be exposed, the physical impact of late pregnancy on lung capacity and the ability to ventilate, inability to use measures such as nursing in the prone position, coupled with low levels of use of evidence-based medical treatment. The other major difference, of course, is the impact on the unborn infant. With around 1 in 5 symptomatic pregnant women giving birth to a preterm baby, this is an important consideration often forgotten at government level.

Andrea Edlow: Pregnant women are more likely than their non-pregnant, age-matched counterparts to require intensive care unit admission (adjusted risk ratio or aRR 3.0), invasive ventilation (aRR 2.9), and extracorporeal membrane oxygenation (aRR 2.4), and are

more likely to die (aRR 1.7) from COVID-19. In addition, data from large epidemiologic studies and meta-analyses suggest specific adverse pregnancy outcomes are more frequent among patients with severe illness, including hypertensive disorders of pregnancy (aRR 1.6), preterm birth (aRR 3.5), caesarean birth (aRR 1.6), and venous thromboembolic disease, among others. While pregnancy itself is a risk factor for disease severity, risk factors for increased severity of COVID-19 within pregnant women include lack of COVID vaccination (more on this below), pre-pregnancy obesity, chronic hypertension, pregestational diabetes mellitus, chronic lung disease, healthcare occupation, and older maternal age, with relative risk of moderate to severe disease increasing steadily with every 5-year increase starting at age 25. There is also likely a trimester-specific risk, with increased risk for severe-critical disease if infection occurs in the third trimester, largely driven by worsening respiratory dynamics and increased cardiopulmonary demands of late pregnancy. Limited data, but data that resonate with clinicians on the ground, suggest that the B.617.1.2 (Delta) variant is associated with a further increase in severe-critical disease, intensive care unit admissions, preterm birth, and caesarean delivery among pregnant women, compared to prior strains including wild type and Alpha. The underlying mechanisms are yet to be elucidated but higher viral load and possibly increased risk of viremia may play a role.

Can you tell us where we are at with the treatment of severe COVID-19 in pregnant women?

Marian Knight: Evidence from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, which included pregnant women, and other trials, on the beneficial treatments for COVID-19 is clear. Steroids, tocilizumab and COVID-19 monoclonal antibody therapies are

beneficial and can be used in pregnancy. However, even critically ill pregnant women are not receiving the same standard of care as non-pregnant women, since the majority do not even receive steroid treatment. Evidence from UK national surveillance of pregnant women hospitalized with COVID-19 shows that only around 40% of those admitted to intensive care received any medical treatment for COVID-19. The UK Confidential Enquiry into Maternal Deaths identified widespread uncertainty among treating clinicians about the safety of medication use for COVID-19 in pregnancy, and a lack of involvement of the wider multidisciplinary team with expertise in pregnancy medicine, who would have been able to provide the relevant expert advice. This is clearly compromising pregnant women's care and may be a reason underlying their poorer outcomes.

Andrea Edlow: Because pregnant women have been excluded from many of the initial COVID treatment trials, and indeed most trials of novel therapeutics, there are more limited data to guide clinicians in this regard. However, clinical trials that have included pregnant women, and observational data outside of trials, have demonstrated the benefit of treating pregnant women with therapies such as steroids and remdesivir. Limited data also suggest a potential benefit of monoclonal antibody therapies (casirivimab/imdevimab for outpatients and tocilizumab for inpatients) and inhaled nitric oxide for pregnant women with COVID-19. At our institution, pregnant women with severe (e.g., oxygen requirement/O_2 saturation $\leq$ 93% on room air) and critical disease are routinely treated with systemic steroids (for up to 10 days) and remdesivir (5 days of therapy). The National Institutes of Health has funded an ongoing trial investigating remdesivir for treatment of COVID-19 specifically in pregnant women, but it bears mention that this trial was not announced until February 2021. While dexamethasone was used in the RECOVERY trial in

non-pregnant individuals, , an alternative regimen was used for the 8 pregnant participants

because this steroid crosses the placenta. One approach taken by our institution and others

is that if steroids are indicated for fetal benefit, we will treat with dexamethasone for 48

hours and then transition to a steroid that does not cross the placenta, such as

hydrocortisone, methylprednisolone, or prednisone. We also consider on a case-by-case

basis whether screening or prophylaxis for latent infections (tuberculosis, strongyloides) is

indicated while on high-dose systemic steroids. At our institution, all pregnant women with

severe or critical disease are also evaluated for possible inhaled nitric oxide therapy.

Depending on disease severity and response to steroids and remdesivir, pregnant women

can be eligible for tocilizumab therapy (if oxygen ≤ 92% on room air and/or escalating

oxygen requirements despite treatment with the above and CRP ≥ 75 mg/L). Regardless of

our institutional policies, we know that at many institutions across the country and world,

pregnant women have not received appropriate medical treatment for COVID-19 due to lack

of comfort and familiarity with treating this population; lack of understanding how

pregnancy physiology may impact disease presentation, evaluation, treatment, and

outcome; and lack of data about safety and efficacy of COVID therapies in pregnant women

specifically. Until research funding for pregnancy and lactation improves and a more

systematic approach is taken to including pregnant women in therapeutic trials, individual

centers publishing case series/case reports with their experience remains a valuable

addition to the medical literature to guide treatment in this understudied group. A multi-

disciplinary approach incorporating pregnancy specialists such as maternal-fetal medicine in

the care of moderate, severe, and critically-ill pregnant women with COVID-19 is critical to

ensuring appropriate and evidence-based care.

What can you tell us about the safety, efficacy and uptake of vaccination during

pregnancy?

Marian Knight: Pregnant women were excluded from vaccine trials until very late, and even

when recommended vaccination, comprehensive data on their outcomes was only collected

in a few areas. Data to advise women has therefore been very patchy. However, it is now

clear, that with more than 250,000 pregnant women vaccinated in the US and UK alone that

there are no safety concerns. The vaccine does not cross the placenta, but we know that

protective antibodies do. Real world data from the UK shows very clear evidence of the

vaccine protecting against hospitalisation and severe disease – 98% of those admitted to

hospital with symptomatic SARS-CoV-2 infection are unvaccinated, and only one woman

who has received both doses of vaccine has required admission to intensive care.

Andrea Edlow: The exclusion of pregnant women from the initial COVID-19 vaccine trials

was disastrous for vaccine confidence among this population known to be at increased risk

for severe disease. Work by our group and others has demonstrated efficacy of the COVID-

19 vaccines in eliciting robust antibody titers in pregnant and lactating women, although

recent data suggest that the kinetics or evolution of the antibody response may be delayed

in pregnant and lactating individuals relative to non-pregnant reproductive age women. In

addition, we and others have shown that vaccine-induced antibodies are transferred to the

fetus and neonate via the umbilical cord and breastmilk. But despite these data on efficacy

and now widespread data on the vaccine's safety in pregnant women, with nearly 172,000

pregnant women vaccinated in the United States and another 100,000 in the UK, COVID

vaccination rates continue to lag among pregnant people relative to the general population.

Vaccination rates among pregnant women continue to hover around 31-32% in the United

States. This vaccine gap continues to drive severe morbidity and mortality in pregnant

women, with August 2021 being the deadliest month of the pandemic in the U.S. for

pregnant women to date—22 maternal deaths. American College of Obstetricians and

Gynecologists and the Society for Maternal-Fetal Medicine issued a joint statement in July

2021 recommending COVID-19 vaccination in all pregnant individuals. In early August 2021,

the CDC endorsed vaccination for all people aged 12 and older, explicitly including people

who are "pregnant, lactating, trying to achieve pregnancy now, or who might become

pregnant in the future." In late September 2021, the CDC issued an urgent alert, strongly

recommending COVID-19 vaccination "either before or during pregnancy because the

benefits of vaccination outweigh known or potential risks." Despite these

recommendations, vaccine hesitancy in the US remains entrenched, and has been

exacerbated within the pregnant population due to inconsistent messaging from clinical

care providers, ease of access to vaccine misinformation and debunked pseudoscience on

social media, and the complex history of racial injustice in science and medicine in the

United States. Indeed, racial and ethnic disparities in COVID-19 vaccination coverage have

been well-described in both pregnant and non-pregnant populations, with vaccine coverage

among Black and Latinx pregnant women one-quarter to one-half of what it is in non–

Hispanic White and Asian pregnant women. If these disparities in vaccination rates remain

uncorrected, they will perpetuate already significant disparities in COVID-19 infections,

hospitalizations, and deaths in communities of color. As obstetric care providers,

understanding the complexity and impact of generations of racism and experimentation

affecting communities of color, particularly women; meeting individuals where they are

with compassion in our vaccine counseling; identifying pragmatic barriers to vaccination;

eliciting patient concerns in a non-judgmental fashion; and assuming that our pregnant

patients share our common goal of ensuring their safety and the safety of their developing

fetus, will go a long way toward alleviating vaccine hesitancy in pregnancy.

Margie Danchin: Maternal vaccination is not new, with years of experience and strong

safety data for both influenza and pertussis vaccines in pregnancy. However, the COVID-19

vaccines present a unique challenge as they are new and have been developed over a

shorter period of time, 9-12 months, compared to longer than traditional vaccine

development timeline of 10-15 years. Many different studies during the pandemic have

consistently identified younger women (between 18 to 40 years) and pregnant, breast

feeding and women planning pregnancy as being less willing to receive a COVID-19 vaccine.

As such, through recent qualitative research to explore the drivers for vaccination for this

group, we found that pregnant women understandably have concerns about the vaccines

and are seeking reputable scientific information on vaccine safety and effectiveness for

themselves and their unborn baby. They are also seeking reassurance on long term

outcomes, particularly for the baby in terms of birth outcomes and on child development,

which is not yet possible as we don't have years of follow up data. Other key concerns are

around fertility for women and men and the impact on women's menstrual cycles. Pregnant

women have also been affected by the changing recommendations for the vaccines in

pregnancy by some professional bodies, such as the Australian Technical Advisory Group on

Immunization, and many express a desire to wait until after the baby is born in case the

recommendations change again. Other pregnant women have felt unduly pressured in

regions where the vaccine has been mandated for health care, essential and educational

workers, which may have eroded their trust in their healthcare provider and the

government. Some pregnant women, despite recognising the higher risk of COVID-19 in pregnancy, don't believe that they will get sick if they stay healthy and don't go out, with a perception of having super-immunity or ways to prevent themselves from becoming infected.

All these concerns underpin the need for effective vaccine communication with pregnant and breast-feeding women to help them to weigh up the risks and benefits. These discussions are most effective with their trusted antenatal healthcare provider, particularly midwives, to provide women with the opportunity to express their concerns without judgement. To tailor these conversations effectively, it is important to understand where on the vaccine acceptance spectrum the women's' attitudes and beliefs may lie, from accepting, hesitant and refusing, as the communication approach differs. With accepting women, informed consent is the aim, whereas with hesitant women we want to carefully elicit all concerns, acknowledge them and facilitate access to trustworthy information, of the appropriate depth that the individual is seeking. At this stage, understanding their motivation to vaccinate can be very helpful. For most pregnant women, their desire to protect their baby is stronger than the desire to protect themselves, so helping them to understand protection for both is crucial. In the discussion, coming back to disease severity helps to shift the focus away from the vaccine alone and the need for vaccination, and lastly, recommending vaccination and explaining where to go, with guidance on how to overcome any practical barriers. If the woman is not ready to vaccinate, it's important to leave the door open as it may take quite a few conversations before she is willing to re-visit her decision.

Other ways to facilitate good communication with pregnant women is to use stories and patient journeys to frame the benefits and risks of COVID-19 vaccination in pregnancy and to understand the personal values that determine how a woman may think, feel and act on risk. These values, such as self-determination, fairness, harm and justice, and are often under-pinned by the heuristics or mental short cuts that we may use to interpret risk, such as availability or omission bias. For example, a serious but rare outcome such as myocarditis after an mRNA vaccine may be given more weighting if it is highly publicized and creates such fear that the person chooses not to vaccinate. Helping people to assess their personal eligibility and weigh the risks and benefit is part of supporting valid consent. Some key principles include communicating the magnitude not acceptability of the risk and to consider using numerical, visual or verbal risk formats to enable a clearer understanding of risk, accounting for health literacy barriers. The broader benefits of vaccination beyond disease prevention, including protection for communities, especially the most vulnerable, establishing vaccination as the social norm, enabling more social mobility such as visiting elderly grandparents, freedom from lockdowns, school closures and the ability to travel, as well as financial security, can also be strong motivators to vaccinate. Lastly, a recommendation from a health care provider is the most important predictor of vaccine acceptance.

Vaccine coverage amongst pregnant women is still much lower than the population average, and varies by state in Australia. To achieve high vaccination coverage in pregnant women, we need to tackle both access or practical barriers as well as acceptance barriers, or questions and concerns about the vaccines. From the evidence we know that education alone is not enough and that multi-component strategies, including nudges such as reminders, vaccine

communication support and training for providers to have effective conversations with pregnant women and educational resources are all needed. It is critical that we consider health literacy and the needs of all cultural groups and that resources are simple, translated and accessible, and that if more detailed information is sought, women know where to go to find the information they are seeking.

What has been the indirect impacts of the pandemic on maternal well-being during pregnancy and childbirth?

Marian Knight: It is clear that the pandemic has had significant impacts on maternal mental health as well as other indirect effects of lockdown measures such as increases in domestic violence. Infection control measures have made responding to other obstetric emergencies more challenging, and we have also seen impacts of remote consultations and concerns over attending hospital, which have led to very late diagnosis of what should be treatable pregnancy conditions. The pandemic has also exacerbated some of the disparities in outcomes for women from different population groups – notably for women from Black and Asian ethnic groups.

Andrea Edlow: The pandemic has served as a sort of stress test for our society, deepening existing inequalities and exposing vulnerabilities in our social and economic systems, with greatest impact on women and girls. The cancellation of in-person school and closing of daycare and other childcare facilities has had a disproportionate impact on women in society, with estimates of between 1.8 and 3 million women dropping out of the U.S. work force, and female labor participation now at a 33-year low in the U.S. For many this change

may be permanent, with wide-ranging consequences for economic security, the gender

wage gap, and access to regular healthcare due to loss of health insurance. Lockdowns have

increased the incidence of intimate partner violence, for which pregnant women are already

at increased risk. In addition, the pandemic has exacerbated disparities in severe maternal

morbidity and mortality among Black and Hispanic women. As prenatal care has shifted to

include many more virtual visits, research efforts have demonstrated racial and ethnic

disparities in the implementation and delivery of telemedicine, as well. Urgent attention

must be paid to mitigating the harms the pandemic has wrought for women in general, and

particularly women from historically underserved racial and ethnic minority groups. Public

policy changes including enhanced access to affordable childcare, support for workforce

reentry programs, and increased funding for medical and scientific research focused on

women and pregnant women, will be key to slowing or reversing some of these harmful

effects.

Caroline Homer: The COVID-19 pandemic has indirectly impacted on every woman giving

birth in 2020 and 2021. There are also considerable inequalities globally that further

increases the impacts. Inequitable access to essential services means that the world will not

meet the Sustainable Development Goals (SDG). This is especially true for SDG 3.1, which

aims to reduce global maternal mortality to less than 70 per 100,000 live births and SDG 3.2,

which aims to reduce neonatal mortality to at least as low as 12 per 1,000 live births by

2030.

There have been considerable disruptions to maternal and newborn health care through

lockdown policies, closure of face-to-face services, especially antenatal and postnatal care,

restrictions on the use of public transport, fears from many people about attending health facilities to give birth, and delays in health seeking behaviours from women. The absence of clear guidelines during COVID-19 and sufficient personal protective equipment have further impacted the delivery of essential services. In many countries there has also been a diversion of maternity staff, initially to work on the COVID-19 wards, and now to administer vaccinations, which has further reduced the ability to provide maternal health care.

Initial fears about the safety of COVID-19 vaccination delayed the immunization of pregnant women in many countries. There are still many countries that have not prioritized pregnant women for the COVID-19 vaccine, which will further contribute to direct deaths and disability and delay the pandemic progress leading to more indirect deaths.

Globally, there are increases being reported in maternal deaths, stillbirth and newborn deaths during the pandemic – not necessarily from COVID-19 but due to the disruptions in care. There are also impacts on the mental health of pregnant and postpartum women and there are likely to be longer term effects on children and families more broadly. Increases in levels of anxiety, depression and fear in pregnant women have been widely reported during the pandemic. A lack of social support from family and friends, financial insecurity and increased caring duties within homes add to the increased risk and development of mental health issues. Many countries have also seen an increase in the risk of intimate partner or domestic violence especially in women from ethnic minorities and marginalized groups. The closure of schools in many countries have led to an impact in education and this will be most profound for girls in the medium to long term, further undoing the advances that have been made. In some countries, the rate of child marriage has increased as parents struggle to cope with

economic losses. More girls exposed to child marriage will ultimately impact on maternal and

newborn mortality and morbidity.

The indirect impacts have not all been negative, especially in some high-income countries.

The visitor restrictions in maternity units have meant many women have said that the

postnatal period has been quiet and peaceful and has enabled them to get to know their

baby without disruptions. Some countries are also reporting reductions in the number of

women giving birth preterm, which may be because of reduction in exposure to pathogens

(like influenza) or reduced stress.

What is the biggest challenge for you in your role in maternal and newborn health during

the pandemic?

Marian Knight: The biggest challenge for me has been trying to be the advocate for the

unrecognized needs of pregnant women at policy level, and the structural biases that still

impact their involvement in research as well as their care. In September 2020 I advocated

for inclusion of pregnant women in vaccine trials, predicting we would be recommending

vaccination to pregnant women with no evidence to support their decision making, a

situation that, sadly, came to pass a few months later. As highlighted above, pregnant

women still do not receive the same standard of care as the non-pregnant population

because of reluctance to treat them and a risk averse culture that does not recognize the

very real benefits of treatment. Vaccination prioritisation decisions have not taken account

of the impact of SARS-CoV-2 infection on preterm birth, focussing solely on mortality rates

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which, for pregnant women in the UK, is still relatively low. I can only hope, at the very least,

that lessons are learned such that in a future pandemic the needs of pregnant women are

recognized and the default for research becomes inclusion rather than exclusion.

Andrea Edlow: The biggest challenge for me as a physician-scientist has been the physical

and emotional toll of caring for critically-ill pregnant patients, coupled with the knowledge

that I could be placing myself and my family at risk for death or severe illness. Even after the

availability of COVID-19 vaccines for adults, for many healthcare workers with young

children who are not yet able to be vaccinated, the constant risk of exposure at work and

elsewhere has weighed heavily. The uncertainty of children's school with unexpected

closures and need for testing due to exposures and/or symptoms has been disruptive to

clinical care and research, with the burden disproportionately shouldered by women

clinicians and scientists. In addition, the pace of COVID-19 research is punishing and

relentless. Studies must be performed rapidly, with large amounts of data 17nalysed and

published quickly to disseminate knowledge to the scientific community, and to ensure

ongoing relevance and novelty of the work. Similarly, keeping up with the pace of new

information, whether new studies or new hospital policies, could itself be a full-time job.

While filling the knowledge gap about COVID-19 and COVID vaccination in pregnancy and

lactation represents a critical mission with great potential impact, the constant uphill swim

against clinical trials and policies that continue to exclude pregnant and lactating individuals

has been frustrating and exhausting.

Caroline Homer: One of the biggest challenges has been finding the evidence to support up to date guidance on the care of pregnant women who contract COVID-19. Clinicians continue to need access to the best evidence to guide clinical care in a fast-moving space. There are literally thousands of papers published on COVID-19 each week and keeping up with these has been very challenging. In Australia, we have been fortunate to have the COVID-19 Clinical Evidence Taskforce, which since March 2020 has produced living evidence-based clinical guidelines that are continually updated.

Another challenge has been to ensure that pregnant women still receive essential services despite the public health measures that reduce access. There is a balance between the provision of services and the exposure of health staff to potential infection, which has been difficult. Millions of health workers around the world have contracted COVID-19 through the course of their work and thousands have died.

Finally, encouraging and enabling pregnant women to be vaccinated has been a big challenge for all midwives. Making sure health workers, especially midwives, obstetricians and family doctors had access to accurate information that they could help women make this important decision has been critical. Addressing the mis-infodemic and addressing fear and hesitancy in a kind and supportive way has been important.

Margie Danchin: Improving vaccine uptake among pregnant, breast feeding and women planning pregnancy will be an ongoing challenge and highlights the ongoing systematic and acceptance issues that surround maternal vaccination. In Australia, we need consistent national data to ensure capture of vaccine uptake in pregnant women through the

Australian Immunisation Register, where pregnancy status is still not recorded for women and most jurisdictions rely on state-based perinatal datasets. Access barriers persist, especially in the public antenatal system where vaccines are often not provided on-site, with an urgent need to ensure vaccines are easily accessible for pregnant women. Mandates have eroded trust amongst providers in jurisdictions where they have been broadly introduced and, with more maternal vaccines in the pipeline, such as group B streptococcus and respiratory syncytial virus, there is an urgent need for comprehensive maternal vaccine communication and education platforms to overcome misinformation and hesitancy and optimize vaccine confidence and uptake. Lastly, in preparation for future pandemics, we need to ensure pregnant women are not excluded from the initial vaccine clinical trials and that we continue to collect the long-term data on maternal health and wellbeing and child development that will answer these pressing questions for expectant parents.
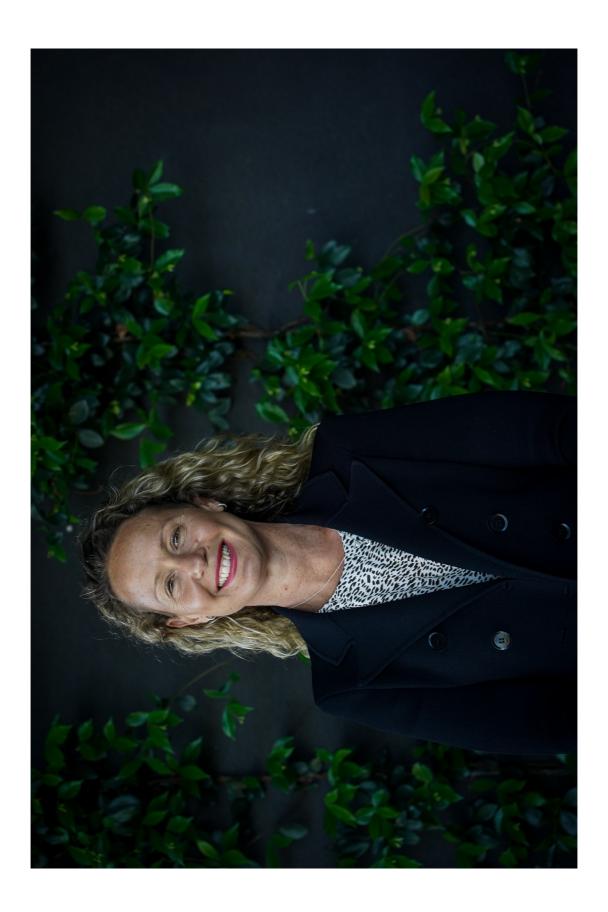
Professor Marian Knight

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Prof Caroline Homer

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Assistant professor Andrea Edlow