

Fertility rates and birth outcomes after ChAdOx1 nCoV-19 (AZD1222) vaccination

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Fears of adverse effects of COVID-19 vaccination on fertility have affected vaccine uptake in some communities. Despite the lack of supporting evidence for such a risk, limited biological plausibility, and recent preliminary data supporting the safety of mRNA vaccines in pregnancy^{1,2,3}, this claim has become widespread, and has been challenged by the World Health Organisation⁴. Vaccine hesitancy during pregnancy, or among women of childbearing age, could have significant public health consequences, as infection with SARS-CoV-2 during pregnancy is a risk factor for severe maternal illness and complications^{5,6}.

Here we report an analysis of the pregnancies that occurred in four ongoing phase I/II/III clinical trials of ChAdOx1 nCoV-19 (AZD1222)⁷, in three countries (UK – NCT04324606, NCT04400838; Brazil - NCT04536051; and South Africa - NCT04444674). These recruited non-pregnant participants to receive the ChAdOx1 nCoV19 vaccine or the control vaccine. Pregnancy was an exclusion criterion in all four studies and all female volunteers tested negative for urine beta-human gonadotrophin (β -HCG) prior to vaccination. Any pregnancies that occurred after vaccination were recorded and followed until 3 months post birth. Pregnancy outcomes were reviewed by the independent DSMB.

A total of 121 participants, out of 9755 women of childbearing age (defined as ≤ 49 years), reported a pregnancy during the trials. The fertility outcome analysis set comprised 93 pregnant women (50 vaccinees and 43 controls). The pregnancy outcome analysis set comprised 107 women (72 vaccinees & 35 controls) (**Figure S1**). Miscarriage was defined as pregnancy loss before 23 weeks gestation. Baseline characteristics were largely comparable between vaccinees and controls, with differences in age and in current alcohol use being more marked (**Table S1**).

There was no evidence for any association between reduced fertility and vaccination with ChAdOx1 nCoV-19 ($p=0.534 - 0.798$, **Table 1a**). (**Table S2** shows fertility rates by site). Analysis of pregnancy outcomes (**Table 1b**) excluded those in the control groups who received either ChAdOx1 nCoV-19 or an mRNA vaccine as part of the national roll-out (after unblinding and during pregnancy; $n=14$, **Table S1**). 56/107 (52%) of the pregnancies in the pregnancy outcome analysis set were on-going at the time of data lock (1st July 2021).

Notably, the rate of miscarriage was not higher in vaccine compared with control arm, with a risk ratio of 0.67 ($p=0.505$), with no material change when analysis was adjusted for the effect of possible confounders, the risk ratio remaining below but closer to unity at 0.84 (**Table S3**). There were 15 live births at the time of analysis and all three preterm births in the vaccinated group were in the late preterm stage (34-37 weeks gestation). There were no stillbirths or neonatal deaths reported in either group.

Table 1. Fertility rates (1a) and pregnancy outcomes (1b) in ChAdOx1 nCoV-19 vaccinated women compared to controls.

1a				Fertility rate ratio	
Site	Parameter	Vaccine (n=4925)	Control (n=4830) **	Vaccine/Control (95% CI)	Exact p value
All sites	Pregnant women *	50	43		
	Fertility Rate	0.0102	0.0089	1.14 (0.76, 1.71)	0.534
	Viable pregnancies ***	32	29		
	Fertility Rate (viable pregnancies)	0.0065	0.0060	1.08 (0.66, 1.79)	0.798
* 28 pregnant women (6 controls & 22 vaccinees) were excluded from this fertility analysis because they were unblinded to vaccine allocation before becoming pregnant. **11 women vaccinated during pregnancy were included in the controls (8 received ChAdOx1 nCoV-19, 3 mRNA vaccines); *** "Viable pregnancies" did not include pregnant women who had a termination or miscarriage.					
1b				Risk Ratio	
Site	Pregnancy Outcome	Vaccine (n=72)	Control (n=35)	Vaccine/Control (95% CI)	Exact p value
All sites	Miscarriage (excluding-Brazil)	6/43 (13.95%)	5/24 (20.83%)	0.67 (0.23, 1.97)	0.505
	Termination (excluding-Brazil)	8/43 (18.60%)	6/24 (25.00%)	0.74 (0.29, 1.89)	0.547
	Miscarriage or Termination [#]	23/72 (31.94%)	13/35 (37.14%)	0.86 (0.50, 1.49)	0.665
	Preterm births	3/10 (30%)	0/5 (0.00%)		
	Full term births	7/72 (9.72%)	5/35 (14.29%)	0.68 (0.23, 1.99)	0.522
	Ongoing pregnancy	39/72 (54.17%)	17/35 (49%)	1.12 (0.75, 1.67)	0.681

14 subjects were excluded from this outcome analysis. These 14 included the 11 from Table 1a (**) who were vaccinated during pregnancy plus 3 additional subjects who received an mRNA vaccine before pregnancy. Risk analysis not adjusted for possible effect of confounders (see **Table S2** for repeat adjusted analysis).

No terminations of pregnancy were reported in Brazil. However, termination of pregnancy is illegal in Brazil and therefore there remains uncertainty as to whether reports of early pregnancy losses were true miscarriage. In view of this, a combined analysis of either miscarriage or termination was conducted for all sites ([#]), with separate sub-group analyses for termination alone and miscarriage alone excluding the Brazilian data. This sub-group contained 24 participants in the control arm and 43 participants in the vaccine arm.

These data show that fertility was unaffected by vaccination with ChAdOx1 nCoV-19. Moreover, there was no increase in risk of miscarriage and no instances of stillbirth in women

vaccinated pre-pregnancy in global clinical trials, compared with those who received the control vaccine.

With ever-greater availability of misinformation, which continues to affect vaccine uptake, these data, along with recent published data on mRNA vaccines^{2,3}, can provide evidence to support women in making decisions regarding vaccination.

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Conflict of Interest Statement

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. AJP is Chair of the UK Department of Health and Social Care's Joint Committee on Vaccination & Immunisation, but does not participate in discussions on COVID-19 vaccines, is a member of WHO's Strategic Advisory Group of Experts, and a UK National Institute for Health Research (NIHR) Senior Investigator.

All other authors declare no competing interests. The members of the Oxford COVID Vaccine Trial Group are listed in the Supplementary Materials.

Author Contributions Statement

KH accessed, verified and analysed the data, performed a literature search and wrote the original draft of the manuscript; SCC and SAM were site principal investigators and collected data; MV advised on data analysis; AJP conceived the study; AMM verified, analysed and interpreted the data, reviewed and edited the manuscript. All authors critically reviewed and approved the final text. AMM and AJP were responsible for the decision to submit the manuscript.

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