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Major article

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Targeted pregnancy and HIV prevention risk-reduction counselling for young women: lessons learned from biomedical prevention trials

Running Title
HIV and pregnancy risk-counselling in prevention trials

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Article summary

Women enrolled in HIV prevention biomedical trials in KwaZulu-Natal, South Africa between 2022-2012 have overlapping risk factors for pregnancy and HIV incidence. This finding emphasizes an urgent need for appropriate, targeted, individual-centred counselling for women participating in HIV prevention trials.

Abstract

Background

Women enrolled in HIV prevention efficacy trials, are counselled at every visit on prevention of HIV, STIs and pregnancy. Incident pregnancy impacts on efficacy outcomes. Incidence rates of pregnancy and HIV/STIs among women who became pregnant and associated risk factors were assessed.
Methods
Data from 9165 women participating in HIV prevention trials in KwaZulu-Natal, South Africa, from 2002-2012 were combined. Demographic and behavioural predictors of incidence pregnancy and incidence HIV and STIs were determined using Cox regression models.

Results
Overall pregnancy incidence was 9.6 per 100-person year (py) (95% CI: 9.1, 10.3). HIV incidence among pregnant women was 5.93 per 100-py (95% CI: 4.73, 7.44). Incidence of STIs among pregnant women for Chlamydia trachomatis, Trichomonas vaginalis, Neisseria gonorrhoeae, and Treponema pallidum (syphilis) were 10.87, 7.42, 3.92 and 1.43 per 100-py, respectively. In the adjusted analyses, we observed overlapping risk factors for HIV acquisition during pregnancy i.e. young age, not married/not cohabitating and low parity. Young women (<20 years of age) were over 3 times at higher risk of pregnancy and HIV acquisition.

Discussion
We identified overlapping risk factors for pregnancy and HIV incidence, suggesting an urgent need for appropriate, targeted, individual-centred counselling for women participating in HIV prevention trials.

Key words
Pregnancy; HIV; STIs; HIV-prevention trials; risk-reduction counselling
Introduction
Approximately 270 000 people were newly infected with human immunodeficiency virus (HIV) in South Africa in 2016 [1]. The province of KwaZulu-Natal had the highest burden of HIV in 2015, with an estimated prevalence rate of 44.4% among antenatal attendees [2]. In the general population, the HIV prevalence and incidence in South Africa is high [3-5]. Risk factors for HIV acquisition during pregnancy, breastfeeding and the postpartum period are reported to be attributed to biological (e.g. elevated hormonal levels, immunological fluctuations and changes in the vaginal microbiome) [6-11] and behavioural risks (e.g. increased frequency of unprotected sexual intercourse and partner infidelity) [12-16]. Additionally, structural risk factors for HIV acquisition include being young, unmarried and not cohabiting with a stable/regular partner [17].

In addition to HIV, four curable STIs viz., *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum* (syphilis), and *Trichomonas vaginalis* continue to be endemic in South Africa [18-22]. In women, STIs have been associated with pelvic inflammatory disease, infertility, cervical cancer, ectopic pregnancy, miscarriage as well as foetal and neonatal death [23, 24]. STIs have been shown to enhance HIV acquisition and transmissibility with mechanisms including increased rate of HIV shedding in persons with concurrent infections [25-27]. A study conducted in Malawi by Taha et al., suggest that STIs such as *Neisseria gonorrhoeae* and *Trichomonas vaginalis* were associated with increased risk of HIV acquisition during pregnancy and the postpartum period. The risk was 2-fold higher for *Trichomonas vaginalis* and 4-fold higher for *Neisseria gonorrhoeae* [28].
Significant investments are made to test new biomedical interventions to prevent HIV among women in our setting, due to the high prevalence and incidence of HIV in South Africa [3-5]. Thus, we have been actively involved in several large scale, multi-centre HIV prevention clinical trials, investigating the efficacy of women-initiated biomedical interventions viz., vaginal microbicides and pre-exposure prophylaxis (PrEP), with limited success [29-36]. Typically, these HIV prevention trials enrol woman aged between 18-45 years, who are not intending to get pregnant but are at high-risk of HIV acquisition. Given the limited data on incidence of pregnancy and concomitant incidence of HIV/STIs among pregnant women in a clinical trial setting, we used the opportunity to combine data from cohorts of women participating in HIV prevention trials, to better understand the rates of incident pregnancy as well as the rates of incident HIV/STIs in women who became pregnant. We hope the data will be useful for future clinical trial design and conduct as well as for local HIV/STI programmatic awareness in antenatal and family planning clinics.

Methods

Study population and procedures

Data from 9165 consenting women enrolled in five phase II/III HIV prevention biomedical trials were combined. A detailed description of the study populations, the diagnostic tests used for HIV/STI testing as well as pregnancy determination has been described elsewhere (see Supplementary table S2) [29-31, 35, 36]. The main eligibility criteria were consistent across the trials; women aged 18 years or older, being sexually active, an HIV negative result at screening and enrolment, a negative pregnancy test, no intention to become pregnant throughout the study,
willing to provide written informed consent, follow study procedure and reside in and around the study area for a minimum of one year. HIV positive women at screening were referred to the local health care facilities for care and support. Women who seroconverted during the trial remained in the study and received ongoing counselling and were referred to local health care facilities for further care at the end of the study. At enrolment and at each follow-up visit, participants were tested for other curable STIs including *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum* (syphilis), and *Trichomonas vaginalis*. Those who tested positive were treated prior to enrolment according to the study protocols and treatment was provided conferring to the local South African guidelines. Women who were free of any STIs were enrolled in the trials. Women were also tested for HIV and pregnancy, received a pelvic examination and were offered contraception free of charge at the site. Women were compensated with the amount of R150 for their time, travel and refreshments. The protocol and informed consent forms were approved by the local ethics committee.
Risk factors and statistical analysis

We considered a wide range of common socio demographic and behavioural risk factors across trials for incident pregnancy and HIV including age at baseline (<20, 20-29, and 30+), marital/cohabitation status (yes/no), level of education (none, primary school, secondary school), contraceptive method (injectable contraception and other forms), parity (0, 1, 2+), and the number of sex partners in the last 3 months (1/2+). Time to pregnancy was calculated as the difference between the date of pregnancy and date of enrolment. Time of pregnancy was defined as the midpoint between the last negative and first positive pregnancy test result. Time to STI positivity was calculated as the time elapsed from enrolment to first positive STI diagnosis (defined as the midpoint between the last negative and first positive STI test result).

Kaplan-Meier curves were used to present the crude incidence rate of pregnancy, and the log rank test was used to test whether incidence differed between groups including age and parity. Cox proportional hazards regression was used to identify the predictors of incident pregnancy and HIV respectively. Multivariate models were created using the variables with P<0.1 in univariate analyses and used forward stepwise methods to finalize the multivariate models. Final multivariate models included only statistically significant factors with P<0.05. Adjusted hazard ratios (aHR) and their 95% confidence intervals were presented from the multivariable analyses. All analysis was performed using Stata 14.0.

Estimating population attributable risk percentage (PAR %)

The PAR% was used to quantify the impact of numerous factors on incidence of pregnancy i.e. proportion of pregnancy cases attributed to various risk factors after adjusting for potential
confounders. Briefly, PAR% and its 95% CIs were estimated for the proportion of pregnancies associated with the risk factor(s) of interest. This epidemiological measure was derived by combining the aHRs from the Cox regression models and the estimated prevalence of the risk factors listed in Table 1. PAR% was used to quantify the relative contributions of various factors on pregnancy and HIV incidence. All the analyses were conducted using SAS statistical software version 9.4 (SAS Inc., Cary, NC, USA) (37).

Results

Incidence of pregnancy

Of the 9165 women enrolled, 1034 (11.3%) women had at least one pregnancy during follow-up, with the overall pregnancy incidence rate of 9.6 per 100-person years (py) (95% CI: 9.1, 10.3).

Incidence of HIV and STIs

HIV and STI incidence among pregnant and non-pregnant women are presented in Table 1. A total of 75 women who had at least one pregnancy during study follow-ups had incident HIV. The HIV incidence rate among women who became pregnant, expressed as number of pregnancies per 100-py, was 5.93 while the HIV incidence in non-pregnant women was 7.05 per 100-py. A total of 322 and 2537 cumulative STIs were recorded for pregnant and non-pregnant women, respectively. The incidence per 100-py among pregnant women of Chlamydia trachomatis, Trichomonas vaginalis, Neisseria gonorrhoeae, and Treponema pallidum (syphilis) were 10.87, 7.42, 3.92 and 1.43, respectively. Similarly, the incidence of curable STIs among non-pregnant women during these trials were Chlamydia trachomatis 9.78 per 100-py, followed
by *Trichomonas vaginalis* (6.85), *Neisseria gonorrhoeae* (3.79), and *Treponema pallidum* (syphilis) (2.14). STI(s) incidence rates were not statistically significant by pregnancy status. Incidence of syphilis, was slightly lower among pregnant women compared to non-pregnant women (1.43 vs 2.14, p = 0.04). Approximately, a quarter of the women who acquired HIV during the trial were co-infected with at least one other STI (data not shown).

**Predictors of incidence pregnancy and HIV**

In the adjusted analyses, being younger (<20), not married/not cohabiting, using contraceptives other than injectable and low parity (≤1 child) were all identified as independent predictors of pregnancy (Table 2). Young women (<20) were more than 3 times at higher risk of pregnancy compared to women aged 30 or above (p < 0.001). Similarly, relative to women aged 30 or above, women aged 20-29 had a 2.4 times higher risk of pregnancy. Unmarried women/not cohabitating were 30% more likely to have incident pregnancy compared to their married peers (p = 0.001). Women on oral contraceptives or not on any form of contraceptive were more likely to be at risk of incidence pregnancy (p < 0.001). A protective role of injectable contraceptives against pregnancy was also observed (p < 0.001). Women with no children were 2.4 times at higher risk of pregnancy relative to women with 2 or more children, respectively (p < 0.001). Kaplan-Meier curves of pregnancy incidence stratified by a) age and b) parity are presented in Figure 1. The data demonstrate that the probability of incident pregnancy significantly increases after the first year of enrolment. Pregnancy incidence was highest among women aged less than 25 (see Supplementary data, Table S1a) and women with 1 child or no children (see Supplementary data, Table S1b).
We observed statistical significant predictors of HIV incidence during pregnancy including age, marital status, methods of contraception, parity and number of sexual partners (Table 2). Women aged <20 years and 20-29 years were 3.2 and 2.4 times more likely to acquire HIV compared to women aged 30 or above, respectively. Unmarried women/not cohabitating had a 2.2 times higher risk of HIV seroconversion compared to married women/cohabitating (p < 0.001). Women who used progestin injectable contraception, depot-medroxyprogesterone acetate (DMPA), were also at increased risk for HIV (aHR: 1.36, 95% CI: 1.14, 1.63, p < 0.001).

Furthermore, women with a lower parity showed an increased risk of HIV seroconversion (aHR: 1.86, 95% CI: 1.45, 2.38, p < 0.001). Women with multiple sexual partners were significantly at higher risk of HIV seroconversion (aHR: 1.39, 95% CI: 1.08, 1.78, p = 0.01).

The population attributable risks (PAR %) and their 95% CIs are also presented in Table 2. In the adjusted analysis, approximately 50% of the incident pregnancies and HIV seroconversions were associated with younger women aged <30. Being unmarried/not cohabitating was observed as a PAR for incident pregnancies and HIV seroconversions (i.e. 45% and 75%, respectively). Use of injectable contraception at baseline, had profound effects on pregnancy and HIV incidence rates. Fifty-eight percent of the all incident pregnancies were associated with either not using contraceptives, or using pills or other methods of contraception (excluding injectable contraception). On the other hand, use of injectable rather than other methodologies was associated with 20% of the HIV seroconversions. Women with 1 child or no children were likely to have 52% and 47% of the pregnancies and HIV seroconversions, respectively.
Although it was not the focus of the current study, we determined high rates of adverse pregnancy outcomes which may potentially be attributed to very high rates of STIs and HIV among these women. Briefly, out of 1034 pregnancies, 92 (9%) of them resulted with elective abortion. Among the remaining pregnancies (i.e. 942), a total of 131 (15%) adverse events have been observed. Vast majority of these events were identified as miscarriage 92 (70%), 21 (16%) of them were premature but live birth while 18 death/still births have been observed (14%).

**Discussion**

This large study of combined data from several cohorts provide insight and raises concern that despite the counselling and care provided to all participants in clinical trials, the risk of pregnancy, STIs and HIV remained high. Our data suggests the need for more individualized intensive counselling based on women’s needs at different time points of their participation in the trial. While we need to recruit and retain women at risk of HIV acquisition in these trials, we also need to minimize risk factors that lead to attrition or loss of “on product” time which can compromise trial efficacy endpoints. Given that these trials are HIV endpoint driven, women who become pregnant in these trials are required to stop study product until after the end of pregnancy and or breastfeeding period and therefore, do minimize their contribution to efficacy endpoints. Our study underscores the fact that the very group that we are targeting for HIV prevention (young women) are the ones that are likely to become pregnant, go off study product and are likely to acquire HIV during pregnancy. HIV incidence among young women aged between 18-25 years in South Africa is one of the highest in the world [3, 5, 38]. Furthermore, we reported on the incidence of unwanted pregnancies (9% elective abortion) in the same age group and younger is of concern. Overall HIV incidence during pregnancy of 5.93 per 100-py,
was similar to the pooled HIV incidence during pregnancy/postpartum reported in a meta-analysis of 19 cohorts (4.7 per 100-py, 95%CI: 3.3, 6.1 per 100 py) [39]. The incidence of HIV during pregnancy in our study was slightly higher than that reported by Chetty et al., in a survey conducted among women in rural KwaZulu-Natal (5.93 vs 4.5 per 100 py) [40].

Interestingly, we identified overlapping risk factors for HIV seroconversion and incidence of pregnancy such as young age, marital/cohabitating status and parity. Thus, suggesting that behavioural and structural drivers do indeed play a significant role in both pregnancy and HIV acquisition. In agreement with Chetty et al., we show that young women were more likely to acquire both HIV and pregnancy [40]. In our study, young adolescent women under the age of 20 years were 3.2 times at higher risk of pregnancy compared to women 30 years and older. The same cohort was also 3.2 times more likely to acquire HIV, a trend consistent to that reported in another study conducted in KwaZulu-Natal [41]. Comparatively, women who did not become pregnant had an HIV incidence rate of 7.05 per 100-py suggesting that during pregnancy sexual intercourse may be decreased hence the risk is slightly lower or alternately, those women who did not become pregnant were likely to be on a reliable contraception but had a higher incidence of STIs due to risky sexual behaviour. However, we do not know if the women who did not become pregnant were intending to actively become pregnant or had no desire to have a pregnancy.

The rapid increase in the probability of pregnancy after one year of follow-up draws attention to the waning effect of HIV and pregnancy prevention counselling and suggests that more intensive, targeted and tailored counselling is warranted, after the first year of enrolment. In this
regard, we are currently developing a combined risk assessment tool for HIV and pregnancy prevention for clinical trial participants so that individualised and focused counselling strategies may be implemented. We previously reported on an HIV risk assessment tool [42] which is currently being implemented in our HIV prevention vaccine trials. While these risk assessment tools for appropriate and targeted counselling are indeed useful in a clinical trial research setting, we believe that they would be excellent for use in general infectious disease and reproductive health clinics in our setting.

Being unmarried contributed to 45% and 75% of incidence pregnancy and HIV, respectively. Cultural fertility expectations have been suggested to influence the pregnancy incidence in young women [43]. In our setting, due to high levels of poverty and unemployment many men are unable to pay *lobola* (bride price); this may contribute to the high prevalence of unmarried women in the community as well as non-marital fertility. Fertility among South African women has declined over time to an average of 3.5 children per woman, in part due to postponement of childbearing and access to contraception [43]. While there are reports that fertility is stabilizing in older women, in younger women, pregnancy incidence is reported to be around 65 per 1000 aged 15-19 years, with a staggering HIV incidence of 17.2 per 100-py in the same age group [44]. Our findings confirm this report and we agree with Tanser *et al.*, in that young South African women have an 80% lifetime risk of HIV [38]. Parity was a significant risk factor for pregnancy and HIV incidence. Those women who had less than one child were at higher risk of both pregnancy and HIV acquisition. This finding was contradictory to the dose response relationship between gravidity and HIV observed by Chetty *et al.*, where the number of prior pregnancies increased risk of HIV [40]. In a Ugandan study, 1% of pregnant women reported
having multiple partners in the previous year, whereas over a third of male partners of pregnant women, disclosed other sexual partners [12].

We observed high rates of incident pregnancy despite access to contraception at research site and assessing women’s contraception use at each study visit through counselling. These findings underscore the need to provide more in-depth counselling on pregnancy prevention and developing a rapport with the participants allowing for more open and honest dialogue on the women’s reproductive health needs.

Our data showed that approximately 60% of all pregnancies would be avoided if women were using injectable contraception. While using injectable progestin contraception as a family planning method would potentially prevent majority of the pregnancies, it was associated with 20% of HIV acquisitions.

The observed high incidence of Chlamydia trachomatis and Trichomonas vaginalis has also been previously demonstrated in the general population [28], with limited data on STI among pregnant women. Our findings are of grave concern as untreated chlamydial and trichomonas infections are associated with adverse pregnancy and neonatal outcomes including miscarriage, preterm birth and low birth weight [23, 24, 45]. Furthermore, maternal chlamydial infections may result in neonatal conjunctivitis and pneumonia [46]. Currently in South Africa, programs consider HIV prevention but STI prevention counselling is unfortunately forgotten. Reproductive health programs need to give serious consideration to the prevalence and incidence of STI and their sequelae among both pregnant and non-pregnant women.
HIV prevention trials target women at risk of HIV acquisition and the inclusion criteria includes women not being pregnant nor intending to be pregnant during the course of the trial. However, the very population that we target may not benefit from new technology being tested due to high pregnancy rates which may impact on efficacy outcomes. It appears that the desire for a child does indeed increase after 1st year of trial participation. Future trial design and implementation need to consider intensifying pregnancy/HIV/STI prevention counselling and ensure adherence to contraceptive after the first year of study participation especially among women who are nulliparous, unmarried, under the age of 20 years and have incident STIs. Depending on the product being tested, if there are sufficient pre-clinical and clinical data on the safety of the drug during pregnancy, consenting women with incident pregnancy should be allowed to continue on the product with careful monitoring of pregnancy outcomes. These data would be useful when introducing an efficacious product in the general population.

Limitations
A limitation to the study is that our findings are based on women in communities who volunteered to participate in clinical trials and who may consider themselves at risk of HIV acquisition. We cannot generalize these findings beyond this group. However, of note, is that our findings do not differ widely from those in general population surveys. Although all STIs were treated, there was no information on partner treatment or resistance testing conducted during these trials. A recent Kenyan study demonstrated that partner notification and STI treatment was effective, accepted and feasible among pregnant/postpartum women and their partners in reducing recurrent STIs in pregnancy [47].
Conclusion

Given the need to recruit and retain women at risk for HIV, in biomedical HIV prevention trials, a better understanding of the population we target is essential, by assessing their needs and risks for both pregnancy and HIV prevention and providing appropriate individualised education and counselling. HIV prevention trials are costly and require high rates of accrual and retention together with high quality data to measure the desired efficacy outcomes. The high rates of incident pregnancy and incidence of HIV/STIs in the trial population, warrants a change in our counselling approach to address reproductive health and HIV prevention needs of women during the course of their trial participation with a more focussed and targeted approach when the risk is the highest.

Acknowledgements

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Conflict of interest

None declared.
References


34. Microbicides Trials Network (MTN). MTN statement on decision to discontinue use of Tenofovir gel in VOICE, a major HIV prevention study in women. 2011.


Tables

Table 1. HIV and STI incidence in women who became pregnant during the trials compared to those who remained non-pregnant throughout the trials

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pregnant</th>
<th>Incidence (per 100-person years)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria gonorrhoeae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnant</td>
<td>49</td>
<td>3.92</td>
<td>2.97-5.19</td>
</tr>
<tr>
<td></td>
<td>Non-pregnant</td>
<td>363</td>
<td>3.79</td>
<td>3.42-4.20</td>
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<td>Chlamydia trachomatis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Pregnant</td>
<td>131</td>
<td>10.87</td>
<td>9.16-12.90</td>
</tr>
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<td>Non-pregnant</td>
<td>923</td>
<td>9.78</td>
<td>9.18-10.44</td>
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<td>Treponema pallidum</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnant</td>
<td>18</td>
<td>1.43</td>
<td>0.90-2.27</td>
</tr>
<tr>
<td></td>
<td>Non-pregnant</td>
<td>206</td>
<td>2.14</td>
<td>1.86-2.45</td>
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<tr>
<td>Trichomonas vaginalis*</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Pregnant</td>
<td>49</td>
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<td>5.61-9.82</td>
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<td>6.18-7.59</td>
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<td></td>
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<tr>
<td></td>
<td>Pregnant</td>
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<td>5.93</td>
<td>4.73-7.44</td>
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<td></td>
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<td>683</td>
<td>7.05</td>
<td>6.54-7.60</td>
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</table>
Table 2. Predictors of pregnancy and HIV Seroconversion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pregnancy</th>
<th>HIV Seroconversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicator</td>
<td>Total (%)</td>
<td>Adjusted hazard ratio (95 % CI)</td>
</tr>
<tr>
<td>Age group</td>
<td>51 (47, 54)</td>
<td>50 (46, 54)</td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>10.40</td>
<td>3.23 (2.61, 4.00)</td>
</tr>
<tr>
<td>20-29</td>
<td>55.47</td>
<td>2.41 (2.05, 2.83)</td>
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<tr>
<td>30+ years</td>
<td>33.80</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Marital/cohabitation status</td>
<td>45 (40, 51)</td>
<td>75 (70, 78)</td>
</tr>
<tr>
<td>Yes</td>
<td>15.40</td>
<td>1 (reference)</td>
</tr>
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<td>No</td>
<td>84.60</td>
<td>1.34 (1.13, 1.58)</td>
</tr>
<tr>
<td>Education</td>
<td>3 (1, 4)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>54.20</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Primary</td>
<td>41.30</td>
<td>0.94 (0.67, 1.31)</td>
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<tr>
<td>Secondary</td>
<td>4.50</td>
<td>0.91 (0.65, 1.27)</td>
</tr>
<tr>
<td>Contraception</td>
<td>58 (55, 60)</td>
<td>20 (15, 23)</td>
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<tr>
<td>Injectable</td>
<td>51.20</td>
<td>0.24 (0.20, 0.28)</td>
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<tr>
<td>Pill</td>
<td>9.89</td>
<td>1.42 (1.20, 1.70)</td>
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<tr>
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<td>1.20 (1.01, 1.42)</td>
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<td>47 (42, 53)</td>
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<td>0</td>
<td>12.40</td>
<td>2.41 (1.95, 2.97)</td>
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<td>1</td>
<td>43.10</td>
<td>1.08 (0.90, 1.31)</td>
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<td>2+</td>
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<td>1</td>
<td>1 (reference)</td>
<td></td>
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<tr>
<td>&gt;1</td>
<td>13.44</td>
<td>1.27 (0.98, 1.63)</td>
</tr>
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</table>
Figures

Figure 1. Kaplan-Meier survival curves of pregnancy incidence stratified by (a) age and (b) parity.