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Anaemic women are more at risk of injectable contraceptive discontinuation due to side-effects in Ethiopia

Rose Stevens[1†*], Blandine Malbos[2†], Eshetu Gurmu[3], Jérémie Riou[2,4] and Alexandra Alvergne[1,5]

Abstract

Background This paper investigates the importance of women's physiological condition, alongside sociocultural factors, for predicting the risk of discontinuation of the injectable contraceptive due to side-effects in Ethiopia.

Methods Contraceptive calendar data from the 2016 Ethiopian Demographic and Health Survey were analysed. Women aged 15-49 who had initiated the injectable contraceptive in the last two years were included in the analysis (n=1,513). Physiological factors investigated were body mass, iron status, reproductive depletion, and physical strain. After checking for reverse causality, associations between physiological risk factors and discontinuation of the injectable contraceptive due to either side-effects (DSE) or other reasons (DOR) were estimated using multivariate Cox proportional regression analyses.

Results Anaemia status was associated with DSE, but not DOR. Anaemic women were two times more at risk of discontinuation due to side-effects (DSE) compared with non-anaemic women (aHR=2.38, CI=1.41-4.00). DOR was predicted by religion, wealth, and relationship status.

Conclusions Accounting for diversity in physiological condition is key for understanding contraceptive discontinuation due to side-effects. To reduce side-effects, family planning programs might benefit from providing hormonal contraception within an integrated package addressing anaemia.

[1]School of Anthropology and Museum Ethnography, University of Oxford, UK

[2] Micro et Nanomedecines Translationnelles, MINT, UNIV Angers, UMR INSERM 1066, UMR CNRS 6021, Angers, France

[3]Center for Population Studies and Institute of Development and Policy Research, Addis Ababa University, Ethiopia

[4] Département de Biostatistiques et de Méthodologie, Délégation de la Recherche Clinique et de l'innovation, CHU Angers, Angers, France

[5] ISEM, Université de Montpellier, CNRS, IRD, EPHE, Montpellier, France

[*]**Correspondence to:**

Rose Stevens

Email: rose.stevens@sant.ox.ac.uk

[†] Joint first authors

Introduction

Globally, over a third of women discontinue modern contraception within a year of initiating use. In over half of these cases, women will stop due to problems with the method or due to method failure, even when they don't want to have a child (Castle and Askew 2015). Studies in low and middle income countries consistently find that one of the main reasons why women discontinue whilst still in need of contraception is the experience or fear of negative side-effects (Castle and Askew 2015). Hormonal contraceptive side-effects, such as irregular bleeding, headaches, and nausea, can take a heavy toll on women's lives. Yet, why some women experience more side-effects than others has attracted little research to date. Clinical trials are focused on overall side-effects burden rather than interindividual variation (Inoue, Barratt, and Richters 2015) and public health research concentrates efforts on dispelling misconceptions and myths (PATH 2015). There has been comparatively little research into the biological correlates of patterns of diversity in the experience of side-effects, despite suggestions that women in poorer physiological condition may experience a greater burden of side-effects (Vitzthum and Ringheim 2005).

Contraceptive discontinuation has been an increasing priority in family planning policies and research has identified several factors associated with the risk of contraceptive discontinuation, which varies by geography, by method of contraception, and by reasons for which a woman discontinues (Ali, Cleland, and Shah 2012; Castle and Askew 2015). Sociocultural factors are known to impact contraceptive knowledge, attitudes and behaviours in general (Bellizzi et al. 2020), and previous studies have shown that age, education, family size, religion, and wealth all impact the risk of discontinuation (Weldemariam, Gezae, and Abebe 2019; Wang and Hong 2017; Mahumud et al. 2015; Agrahari, Mohanty, and Chauhan

2016). In comparison, the role of physiological factors, such as energy expenditure or nutritional deficiencies, in modulating the risk of discontinuation has been little considered. The focus on sociocultural, rather than biological, drivers of discontinuation is justified by the successes gained by using a social determinants of health framework in public health more generally (Marmot et al. 2012). However, if one is to understand the risk of discontinuation due to side-effects rather than to any other reasons, the importance of physiological factors for shaping the risk of experiencing side-effects ought to be evaluated. A new model, taking into account a potential physiological aetiology, together with sociocultural factors, is needed to explain interindividual variation in the experience of contraceptive side-effects and subsequent risk of discontinuation (Alvergne and Stevens 2021).

A biological perspective suggests that side-effects arise from the interaction of synthetic hormones with women's physiology. Side-effect experiences depend on the concentration of synthetic hormones at targeted and/or non-targeted sites of action, as well as the magnitude of suppression of natural reproductive hormone levels. Women who experience the greatest suppression of their natural reproductive hormones after initiating hormonal contraception are those with the lowest levels of natural reproductive hormones prior to use (Landgren and Diczfalusy 1980). This suppression may cause them to experience more severe side-effects, such as symptoms associated with natural hormone deficiency (e.g. mood swings, headaches, irregular bleeding). Thus, it has been suggested that women with lower levels of natural reproductive hormones may experience more intense/frequent side-effects (Vitzthum and Ringheim 2005), and that diversity in women's reproductive physiology could explain variation in discontinuation due to side-effects. Whilst previous research has considered this link at a population level (Vitzthum and Ringheim 2005), evidence for the relationship

between hormone levels and discontinuation of contraception due to side-effects at the individual level is lacking.

Anthropological studies have shown that usually lower concentrations of reproductive hormones are found among women with poor physiological condition due to energetic and immune stress (Vitzthum 2009; Jasienska 2013), associated with indicators such as high workloads, long times to fetch water, high inflammation or low body size and fat stores. Another indicator of poor condition is anaemia, which might indicate low natural hormone levels. Anaemia can result from environmental and somatic stressors such as iron deficiency, depletion from pregnancy, and/or infection. Anaemia hinders follicle growth in the ovaries (Aleshire et al. 1989), likely leading to lower levels of reproductive hormone production. Though there is a lack of clinical evidence for the relationship between these markers of physiological condition and side-effects, women in qualitative studies regularly cite harsh lifestyle factors and poor diets as predisposing individuals to experiencing contraceptive side-effects (Meskele and Mekonnen 2014; Alvergne, Stevens, and Gurmu 2017).

This paper seeks to investigate whether women's physiological condition is associated with discontinuation due to side-effects (DSE) in the Ethiopian 2016 Demographic and Health Survey (DHS) (Central Statistical Agency (CSA) [Ethiopia] and ICF 2016). Not all variables which may be associated with reproductive hormone levels were available in this dataset, but it provides high-quality large-scale data with detailed contraceptive information and relevant physiological factors. Rates of DSE are high in Ethiopia (about 1 in 5 women reported "side-effects" as the main reason for discontinuation (Central Statistical Agency (CSA) [Ethiopia] and ICF 2016)) despite an extended community-based family planning program. We focus

our analysis on the 3-month injectable contraceptive as it is the most prevalent method in Ethiopia (63%) (Central Statistical Agency (CSA) [Ethiopia] and ICF 2016) and Sub-Saharan Africa (47%) (Tsui, Brown, and Li 2017) and eliminates any confounding by contraceptive method used. It is also consistently associated with the highest rates of DSE (Ali, Cleland, and Shah 2012). To evaluate the role of physiological condition in increasing the risk of DSE specifically, as opposed to any form of discontinuation, we compared the association of markers of physiological condition with both discontinuation due to side-effects (DSE) and discontinuation due to other reasons (DOR). We predicted that measures of physiological stress (low BMI, agricultural occupation, longer time to fetch water, being anaemic, lack of iron supplementation, recent birth prior to injectable initiation) would increase the risk of DSE, but not that of DOR. This knowledge may help devise new solutions tailored to women's bodies to reduce side-effects and improve contraceptive continuation.

Methods

Data and participants

The DHS Program

This study uses secondary data obtained from the DHS program repository. It focuses on the Ethiopian 2016 DHS survey, which was implemented by the Central Statistical Agency (CSA) from January to June 2016 (Central Statistical Agency (CSA) [Ethiopia] and ICF 2016). A total of 16,650 households were successfully interviewed, with a response rate of 98% of occupied households. The DHS survey uses a cross-sectional two-stage cluster sampling approach. Sample weights were employed to obtain population representative results.

Data Collection Methods

Detailed information on lifestyle, health, contraceptive, and reproductive histories were collected for 15,683 women aged 15-49. Histories were collected using the 'reproductive-contraceptive calendar'. This is a month-by-month history of the last 5-6 years preceding the interview of a woman's key reproductive events and has been shown to be of better quality than standard questionnaire methods (Goldman, Moreno, and Westoff 1989). Only one reason per discontinuation event is recorded, precluding any analysis of multifactorial discontinuation decisions. A drop of blood taken from a finger prick was analysed using a HemoCue to measure haemoglobin levels, adjusted for cigarette smoking and altitude (WHO 2001). These adjustments may not be appropriate for certain East African ethnicities (Sarna et al. 2018), but we retained them to allow for comparability with other studies.

Inclusion Criteria

Only women who initiated injectable contraception within two years prior to the interview were included to reduce recall bias and eliminate left censoring. This ensured that biomarker data (taken at interview) such as haemoglobin and BMI were taken a maximum of two years since contraceptive initiation, a period over which they were assumed to be relatively stable. Haemoglobin trajectories have been shown to be relatively consistent during this timeframe (Dayimu et al. 2019). Only the first episode of injectable use in the last two years was included in the analysis. We excluded women who were pregnant at the time of the interview (n=66) and women who answered 'Other' for religion (n=7). A total of 1,513 women aged 15-49 were included in the final analysis (Figure 1).

Variables

Outcome variables:

Our primary outcome variable was whether a woman had discontinued due to side-effects (DSE). Our secondary outcome variable was whether a woman had discontinued due to reasons other than side-effects (DOR).

Independent variables:

We extracted standard sociodemographic variables and known sociocultural risk factors for discontinuation, such as age (15-24, 25-34, 35-49), education (no, primary, secondary+), residence de facto (urban, rural), ethnicity (Amhara, Oromo, Tigrie, Others; 80 levels brought down to 4 based on prevalence), parity (0, 1-2, 3+), religion (Muslim, Orthodox Christian, Catholic and Protestant), household wealth (40% poorest, 20% middle, 40% richest; derived from 5 quintiles using country specific wealth estimates, based on a score derived from various consumer goods owned and housing characteristics), and relationship status (married or cohabiting, not in a relationship).

In order to evaluate the importance of physiological condition, we investigated factors measuring body mass, iron status, reproductive depletion, and physical strain. we extracted the variables height (in cm; using a Shorr measuring board) and weight (in kg; using a SECA scale) to compute BMI (Underweight <18.5, Normal: 18.5-24.9, Overweight ≥25.0), anaemia (Yes, No; classified as anaemic if adjusted haemoglobin was <12g/dl), taken iron supplementation (Yes, No; only collected for supplementation during the most recent pregnancy within the last 5 years; those with no pregnancy coded as not having taken supplements and sensitivity analysis conducted with removal of these individuals to ensure this group did not drive the results), time from most recent birth to injectable initiation (0-2 months, 3-12 months, 13-24 months, >24 months, No births in the last 5 years), time to fetch water (≤20 min, >20min), and occupation (agricultural/non-agricultural/no work).

Statistical analysis

Reverse causality:

An analysis based on weighting propensity score using an Inverse Probability Weighting (IPW) (Rosenbaum and Rubin 1983; Austin et al. 2005) was performed to evaluate the causal impact of currently taking injectables on anaemia and BMI. This weighting created two groups ("current injectable users (minimum 3 months)" versus "had no contraceptive method or pregnancy in the last 24 months"), strictly comparable on all the variables included in the survival analysis to follow (Figure S1). By then comparing the variables of interest in these two groups, this strategy allowed us to envisage whether there was a causal effect of using the injectable on being anaemic or BMI, in order to check that our analyses were not being impacted by reverse causality.

Survival Analysis:

We tested for exposure variables associated with discontinuation due to side-effects (DSE). Our secondary analysis tested for exposure variables associated with the secondary outcome, i.e. discontinuation due to other reasons (excluding side-effects) (DOR). This secondary analysis allows disentangling the effects that are specific to side-effects compared to other reasons for discontinuation. The original research plan was pre-registered with the Open Science Framework (https://osf.io/276gt) and all analyses were performed using the R software (R Core Team 2019).

Descriptive analysis compared distributions of each factor between those with the outcome and those without for both the DSE and DOR analyses using Fisher exact tests. All estimates presented are weighted to account for the DHS sampling design. Weighted multivariate cox regression analyses were used to compare the impact of exposure variables on the risk of either DSE or DOR. Women were right-censored either at the time of the survey or earlier if they discontinued for other reasons. The unit of analysis is an episode (i.e. a month) during which women are 'at risk' of discontinuing. The hazard of an event (i.e. DSE or DOR) is predicted as a function of the duration of injectable use.

Exposure variables associated with either DSE or DOR to $p<0.2$ in univariate Cox regression analyses were investigated in the multivariate Cox regression analysis together with known confounders. To obtain a parsimonious final model, a manual step-down variable selection coupled with a study of the Akaike information criterion (AIC) was performed for each regression model. Variables were dropped individually from the multivariate model until the reduction in AIC was lower than 2 units, to obtain a final model that explained the most variation in the outcome using the fewest parameters. A check for collinearity between the explanatory variables was performed using the variance inflation factor (VIF). Adjusted

hazard-ratios (aHR), 95% confidence interval (CI) and p-value were used to determine the strength of associations. Proportionality was checked using scaled Schonfeld residuals, by both plotting these against time and testing formally for non-proportionality.

All analyses were performed at the Type-I error rate (alpha) of 5 percent. All tests were two-sided. The packages ‘survival”, ‘ggplot2’, ‘WeightIt’, ‘survey’ and ‘missForest” were used (Lumley 2004; Imai and Ratkovic 2013). Due to the prioritization of objectives, no correction for multiple testing was necessary. No data imputation was made.

Results

Descriptive statistics

Among the 1,513 women aged 15-49 who initiated the injectable in the two years preceding the DHS interview, 25.7% discontinued the injectable. Of those who discontinued, 19.9% reported side-effects as their reason for discontinuation, second to wanting to become pregnant (21.9%). Our analysis is minimally affected by missing data (only 1.7% of all data missing), which are not informative (Figures S2 and S3). The descriptive analysis was stratified according to the outcome of interest and differences in subjects' characteristics between groups were analysed using the Fisher exact test for categorical variables (Table 1).

Risk of discontinuation due to side-effects (DSE):

In the adjusted model, anaemic women were at over double the risk of DSE compared to non-anaemic women (aHR=2.38, CI= [1.41-4.00], p=0.001) (Table 2, Figure 2). Women who had given birth either 3-12 months or 13-24 months prior to injectable initiation were at greater risk of DSE as compared with women who had given birth over 24 months ago. Women who had taken iron supplements were at reduced risk of DSE compared to others (aHR=0.54, CI= [0.31-0.96], p=0.036). Finally, as compared to underweight women, overweight women were at greater odds of DSE (aHR=3.90, CI= [1.24-12.23], p=0.020).

The reverse causality analysis revealed that injectable use was associated with both a lower risk of being anaemic and an increased risk of high BMI at interview. Thus, those who were anaemic at the time of interview are unlikely to have become anaemic due to injectable use, strengthening our assumption that women who both DSE and were anaemic were likely anaemic upon injectable initiation. However, as injectable use was associated with higher BMI at interview, overweight women may have been normal weight upon initiation.

Therefore, we maintained BMI as a confounder in both models to adjust for the impact of weight changes associated with injectable use on risk of discontinuation.

Risk of discontinuation due to other reasons (DOR):

To check whether physiological risk factors for DSE were in fact general drivers of discontinuation, independently of side-effects, we ran the same analysis for DOR (Table 2, Figure 3). We found this not to be the case, as only sociocultural risk factors were associated with DOR. Catholics and Protestants have lower odds of DOR than Muslims (aHR=0.41, CI= [0.23-0.74], p=0.003), but there were no differences between Muslims and Orthodox Christians. Wealth is protective for DOR, with the 40% wealthiest (aHR=0.60, CI= [0.40-0.90], p=0.013) having reduced odds of DOR compared to the 40% least wealthy. Those not in a relationship were at over three times more at risk of DOR (aHR=3.50, CI= [2.27-5.39], p<0.001) compared to those in a relationship. DOR results were not driven by women who DSE in the non-DOR comparison group, as the results were not changed when a sensitivity analysis was conducted by removing those who DSE from the comparison group.

Discussion

We investigated whether physiological factors, such as iron status, BMI, reproductive depletion, and physical strain, were associated with the risk of injectable contraceptive discontinuation due to both side-effects (DSE) and other reasons (DOR). Using data from the 2016 Ethiopian Demographic and Health Survey, we found that DSE, but not DOR, was associated with physiological factors likely indicative of low iron status, such as being anaemic, not having received iron supplements and having given birth in the last two years prior to injectable initiation. By contrast, an increased risk of DOR was driven by sociocultural characteristics only, including lower wealth, not being in a relationship and religion. The lack of relationship between physiological risk factors and DOR suggests that side-effects driven discontinuation is at least partly driven by physiology. These results have implications for both family planning provision and discourse around the reasons underpinning side-effects.

The results show that anaemia doubles the risk of discontinuation due to side-effects. This effect cannot be explained by the impact of contraceptive use on anaemia: whilst injectable use was associated with a reduced risk of anaemia, anaemia was not found to be a risk factor for DOR, despite women who DOR having on average shorter durations of contraceptive use compared to women who DSE (6.28 vs. 7.01 months respectively). This suggests that anaemia is an important risk factor for discontinuation due to side-effects specifically, rather than discontinuation due to other reasons. Previous studies showing only sociocultural factors to be associated with risk of discontinuation may have been confounded by their lack of inclusion of physiological factors, such as anaemia, which are associated with sociocultural factors such as wealth (Weldemariam, Gezae, and Abebe 2019).

There are several limitations to our analysis associated with the cross-sectional nature of DHS data. Firstly, the contraceptive calendar is measured retrospectively, making it subject to recall bias and post-rationalization. We minimized this bias by restricting the sample to injectable episodes initiated within the last two years. Second, the analysis relies on the assumption that anaemia at interview is a proxy for anaemia prior to or during contraceptive use. Previous studies (Dayimu et al. 2019) have indeed shown that iron trajectories are fairly stable over time, and the current analysis shows that, if anything, haemoglobin levels increase slightly with injectable use. Therefore, it is reasonable to assume that haemoglobin levels were either similar or lower at the time of injectable initiation.

The results support the role of iron levels *prior* to contraceptive initiation in shaping the risk of DSE. Firstly, having taken iron supplementation during the most recent pregnancy is protective of DSE. Secondly, women who initiated injectable use less than two years after their last birth had higher risk of DSE. High levels of iron are lost during pregnancy, leading to depleted iron stores after birth, particularly so for short interbirth intervals (Miller 2016) and for women who did not take iron supplements. Women who have more depleted iron stores after birth may thus experience a greater burden of side-effects. One exception is that women who had given birth 0-2 months before initiating the injectable also had lower risk of DSE. This may be due to an increased motivation to avoid pregnancy very soon after giving birth. As a proportion of the sample had not given birth in the last 5 years and no data on iron supplements uptake during the last pregnancy were available, a sensitivity analysis only including women with births in the last 5 years was run. We found that the effect of iron supplementation remained unchanged. The effects of iron supplementation and time since birth before initiation also remained after adjusting for haemoglobin levels, suggesting that depleted iron stores, independently of haemoglobin levels, may themselves also contribute to

side-effects. Multiple measures of iron status, capturing iron stores and bioavailability, are thus needed to understand what may be driving side-effects.

Taken together, our findings point towards iron-deficiency anaemia specifically as a driver of DSE. Anaemia may be caused by nutritional deficiencies, pregnancy depletion or blood loss (iron deficiency anaemia (IDA)), or immune stress causing iron withholding (anaemia of infection (AI)). Our finding that iron supplementation is protective of DSE suggests that iron-deficiency anaemia is particularly important for DSE. If the relationship between anaemia and DSE was driven instead by anaemia of infection, which is characterized by iron withholding and decreased iron absorption due to increased levels of the enzyme hepcidin (Chaparro and Suchdev 2019), we would not expect to see an effect of iron supplementation on DSE. Future analyses should include biomarkers of immune stress and additional measures of iron status to understand if anaemia is caused by iron deficiency or iron withholding.

One potential explanation for why low iron increases the risk of DSE is that, if there is a relationship between iron status and reproductive hormones levels, women with lower iron levels would likely experience the most side-effects from typically high contraceptive doses (Vitzthum and Ringheim 2005). Whether low iron is indeed associated with lower reproductive hormone levels remains to be further investigated (Miller 2016). Studying the response of anaemic and non-anaemic women to different doses of contraception, such as the lower dose injectable, Sayana Press, may present a promising avenue for understanding the interaction of dose, hormone levels, iron, and side-effects.

The association between iron status and DSE has potentially important implications for both family planning programs and contraceptive discontinuation research. First, family planning programs might benefit from providing an integrated service package addressing anaemia together with hormonal contraception, whereby counselling prior to prescription of contraceptives could add a haemoglobin test. If anaemia is detected, the cause of low haemoglobin could be investigated and treated. Second, new data are needed to capture the heterogeneous phenomenon that is discontinuation, which is not currently measured in a nuanced way (Inoue, Barratt, and Richters 2015). Those include prospective longitudinal data on multiple discontinuation reasons per event, data on types of side-effect experiences, and physiological data, such as iron levels, body fat and hormones. Once such data is available, conducting path analyses or structural equation modelling may help unpick relationships between sociocultural and physiological factors, and their relative contribution to side-effect experiences. Understanding the causal relationships between physiological factors and side-effects may not only help reduce discontinuation, but also stimulate research to improve contraceptive technology and service quality for women. This utilises a rights-based, quality of care approach (Hardee et al. 2014) by focusing concurrently on quality of life during use and helping women achieve their fertility goals through either continuation or timely discontinuation of their method of contraception.

Data Availability

All data used in the analyses are available from https://dhsprogram.com/ upon request.

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Ethics approval and consent statement

Procedures and questionnaires for standard DHS surveys were approved by the ICF Institutional Review Board (IRB) and the specific Ethiopian protocol was approved according to local guidelines by the IRBs of the Federal Democratic Republic of Ethiopia Ministry of Science and Technology. An informed consent statement was read to the respondents before the interview and all participants provided voluntary informed consent.

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Author contributions

RS and AA developed a proposal and study design for the analysis, with input from EG. RS and BM undertook the literature search. JR did most of the statistical analysis. RS, AA and BM contributed to drafting the manuscript. JR and EG reviewed the manuscript and provided feedback and additions.

Competing Interests

The authors declare there are no competing interests.

TABLE 1 Weighted descriptive table of the sample for all variables included in the analysis. DSE: Discontinuation due to side-effects. DOR: Discontinuation due to other reasons. The p-values indicate the significance of Fisher exact tests. n weighted = 1925. n unweighted = 1513.

	TOTAL		Comparison between NON-DSE and DSE			Comparison between NON-DOR and DOR		
	Unweighted n (%)	Weighted n (%)	NON-DSE n (%)	DSE n (%)	p-value	NON-DOR n (%)	DOR n (%)	p-value
Sociodemographic factors								
Age group					0.096			<0.001
15 - 24	597 (30%)	655 (34%)	637 (35%)	18 (23%)		517 (32%)	138 (45%)	
25 - 34	654 (43%)	880 (46%)	837 (45%)	43 (54%)		763 (47%)	116 (38%)	
35 - 49	262 (17%)	390 (20%)	372 (20%)	18 (23%)		336 (21%)	53 (17%)	
Area					0.670			0.521
Urban	466 (31%)	356 (19%)	343 (19%)	13 (17%)		1321 (82%)	247 (80%)	
Rural	1047 (69%)	1568 (81%)	1503 (81%)	65 (83%)		295 (18%)	61 (20%)	
Parity					0.106			<0.001
0	243 (16%)	253 (13%)	248 (13%)	5 (6%)		189 (12%)	65 (21%)	
1 - 2	635 (42%)	711 (37%)	685 (37%)	26 (34%)		574 (34%)	137 (44%)	
3+	635 (42%)	959 (50%)	913 (49%)	46 (60%)		853 (53%)	106 (34%)	
Wealth index					0.175			0.007
40% poorest	435 (29%)	610 (32%)	582 (32%)	28 (36%)		489 (30%)	121 (40%)	
40-60%	277 (18%)	438 (23%)	427 (23%)	11 (14%)		375 (23%)	64 (21%)	
40% richest	801 (53%)	876 (46%)	837 (45%)	39 (50%)		752 (47%)	123 (40%)	
Education					0.618			0.928
No education	634 (42%)	981 (51%)	938 (51%)	43 (56%)		822 (51%)	159 (52%)	
Primary	567 (37%)	672 (35%)	649 (35%)	23 (30%)		565 (35%)	107 (35%)	
Secondary+	312 (21%)	270 (14%)	259 (14%)	11 (14%)		228 (14%)	41 (13%)	
Religion					0.620			<0.001
Protestant + Catholic	329 (22%)	497 (26%)	480 (26%)	17 (22%)		464 (29%)	33 (11%)	
Muslim	376 (25%)	463 (24%)	445 (24%)	18 (23%)		389 (24%)	74 (24%)	
Orthodox	808 (53%)	964 (50%)	921 (50%)	43 (55%)		763 (47%)	201 (65%)	
Ethnicity					0.053			<0.001
Amhara	505 (33%)	697 (36%)	675 (37%)	22 (29%)		552 (34%)	145 (47%)	
Oromo	329 (22%)	559 (29%)	534 (29%)	25 (32%)		486 (30%)	73 (24%)	
Tigrie	257 (17%)	172 (9%)	159 (9%)	13 (17%)		129 (8%)	43 (14%)	
Others	422 (28%)	495 (26%)	478 (26%)	17 (22%)		448 (28%)	47 (15%)	
Desire for a child					<0.001			<0.001

No	515 (34%)	742 (39%)	726 (39%)	16 (21%)		650 (40%)	92 (30%)	
Wants after 2+ years	757 (50%)	943 (49%)	902 (49%)	41 (53%)		785 (49%)	158 (51%)	
Wants unsure of timing	53 (4%)	56 (3%)	48 (3%)	8 (10%)		43 (3%)	12 (4%)	
Wants within 2 years	188 (12%)	183 (10%)	170 (9%)	13 (17%)		137 (9%)	46 (15%)	
Relationship					0.716			<0.001
Not in a relationship	160 (11%)	170 (9%)	164 (9%)	6 (8%)		1519 (94%)	234 (76%)	
Married or cohabiting	1353 (89%)	1754 (91%)	1682 (91%)	72 (92%)		97 (6%)	73 (24%)	
Physiological factors								
Anaemia[†]					0.007			0.427
No (>=12 g/dl)	1175 (81%)	1514 (81%)	1462 (82%)	52 (69%)		1277 (81%)	237 (80%)	
Yes (<12 g/dl)	272 (19%)	351 (19%)	328 (18%)	23 (31%)		290 (19%)	61 (20%)	
BMI (kg/m²)					0.852			0.002
<18.5	283 (19%)	363 (19%)	350 (19%)	13 (17%)		282 (18%)	80 (27%)	
18.5 – 24.9	1044 (72%)	1405 (75%)	1347 (75%)	58 (76%)		1200 (76%)	205 (68%)	
≥ 25	134 (9%)	108 (6%)	103 (6%)	5 (7%)		93 (6%)	16 (5%)	
Time to get water					0.226			0.072
≤ 20min	871 (60%)	1013 (55%)	979 (55%)	34 (48%)		837 (54%)	176 (60%)	
>20min	577 (40%)	832 (45%)	795 (45%)	37 (52%)		714 (46%)	119 (40%)	
Occupation					0.111			0.151
Agricultural work	323 (22%)	434 (23%)	409 (23%)	25 (33%)		357 (23%)	77 (25%)	
Not working	687 (47%)	953 (51%)	919 (51%)	34 (45%)		815 (51%)	138 (45%)	
Non-agricultural work	462 (31%)	499 (26%)	482 (27%)	17 (22%)		411 (26%)	89 (29%)	
Time since last birth to injectable initiation					0.003			<0.001
0-2 months	440 (29%)	556 (29%)	544 (30%)	12 (16%)		485 (30%)	71 (24%)	
3-12 months	321 (22%)	430 (23%)	406 (22%)	24 (32%)		364 (23%)	66 (23%)	
13-24 months	226 (15%)	315 (17%)	294 (16%)	21 (28%)		275 (17%)	40 (14%)	
> 24 months	162 (11%)	211 (11%)	207 (11%)	4 (5%)		187 (12%)	25 (9%)	
No births in last 5yrs	347 (23%)	394 (21%)	380 (21%)	14 (19%)		303 (19%)	91 (31%)	
Iron supplementation with last pregnancy					0.013			0.003
Not taken	825 (57%)	1080 (59%)	1029 (58%)	51 (73%)		908 (57%)	173 (67%)	
Taken	616 (43%)	764 (41%)	745 (42%)	19 (27%)		678 (43%)	86 (33%)	

[†]Respondents were classified as anaemic if their haemoglobin levels were below 12 g/dl when adjusted for altitude of residence.

TABLE 2 Adjusted hazard ratios from the final Cox model investigating the impact of different factors on the risk of discontinuation due to side-effects (DSE) using weighted estimates.

	Event: Discontinuation due to side-effects		
	Adjusted HR	**95% CI**	**p-value**
Anaemia[†]			
No (>=12g/dl)	*ref*		
Yes (<12 g/dl)	2.38	1.41- 4.00	0.001**
Time since last birth to injectable initiation			
0-2 months	*ref*		
3-12 months	3.26	1.60-6.61	0.001**
13-24 months	2.82	1.32-6.05	0.008**
> 24 months	0.95	0.26-3.45	0.934
No births in last 5 yrs	1.12	0.48-2.60	0.798
Iron supplementation with last pregnancy			
Not taken	*ref*		
Taken	0.54	0.31-0.96	0.036*
BMI (kg/m^2)			
< 18.5	*ref*		
18.5 – 24.9	1.89	0.92-3.89	0.084
≥ 25	3.90	1.24-12.23	0.020*

*Exposure variables associated with DSE to p<0.2 in univariate Cox regression analyses considered in the full model before step down variable selection were anaemia status, time since last birth to injectable initiation, iron supplementation with last pregnancy, ethnicity, occupation, BMI, parity, and age group. The estimates presented here are for those variables remaining in the final model mutually adjusted for each other. [†]Respondents were classified as anaemic if they haemoglobin levels were below 12 g/dl when adjusted for altitude of residence. *p<0.05, **p<0.01, ***p<0.001. HR = hazard ratio.*

TABLE 3 Adjusted hazard ratios from the final Cox model investigating the impact of different factors on the risk of discontinuation due to other reasons (DOR) using weighted estimates.

	Event: Discontinuation due to other reasons		
	Adjusted HR	**95% CI**	**p-value**
Relationship	..		
Married or cohabiting	*ref*		
Not in a relationship	3.50	2.27-5.39	<0.001 ***
Wealth	..		
40% poorest	*ref*		
20% middle	0.69	0.45-1.06	0.092
40% richest	0.60	0.40-0.90	0.013*
Religion			
Muslim	*ref*		
Catholic + Protestant	0.41	0.23-0.74	0.003***
Orthodox Christian	1.13	0.74-1.73	0.573
BMI (kg/m^2)			
< 18.5	*ref*		
18.5 – 24.9	0.73	0.49-1.08	0.112
≥ 25	1.06	0.55-2.05	0.866

*Exposure variables associated with DOR to p<0.2 in univariate Cox regression analyses considered in the full model before step down variable selection were relationship, ethnicity, wealth index, religion, time to get water, parity, BMI, age group, time since last birth to injectable initiation and iron supplementation with last pregnancy. The estimates presented here are for those variables remaining in the final model mutually adjusted for each other. *p<0.05, **p<0.01, ***p<0.001. HR = hazard ratio.*

FIGURE 1 Sample flow chart showing inclusion criteria

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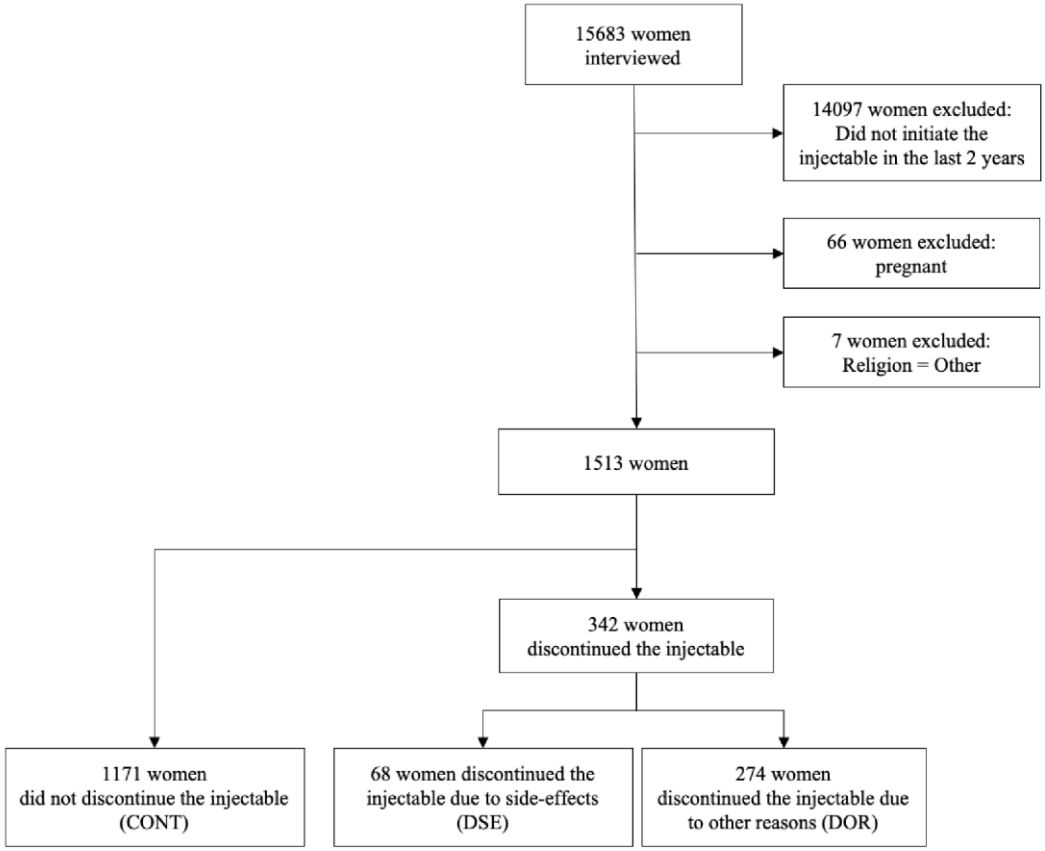

FIGURE 2 Adjusted hazard ratios and 95% CI for the association between each factor and risk of discontinuation due to side-effects (DSE)

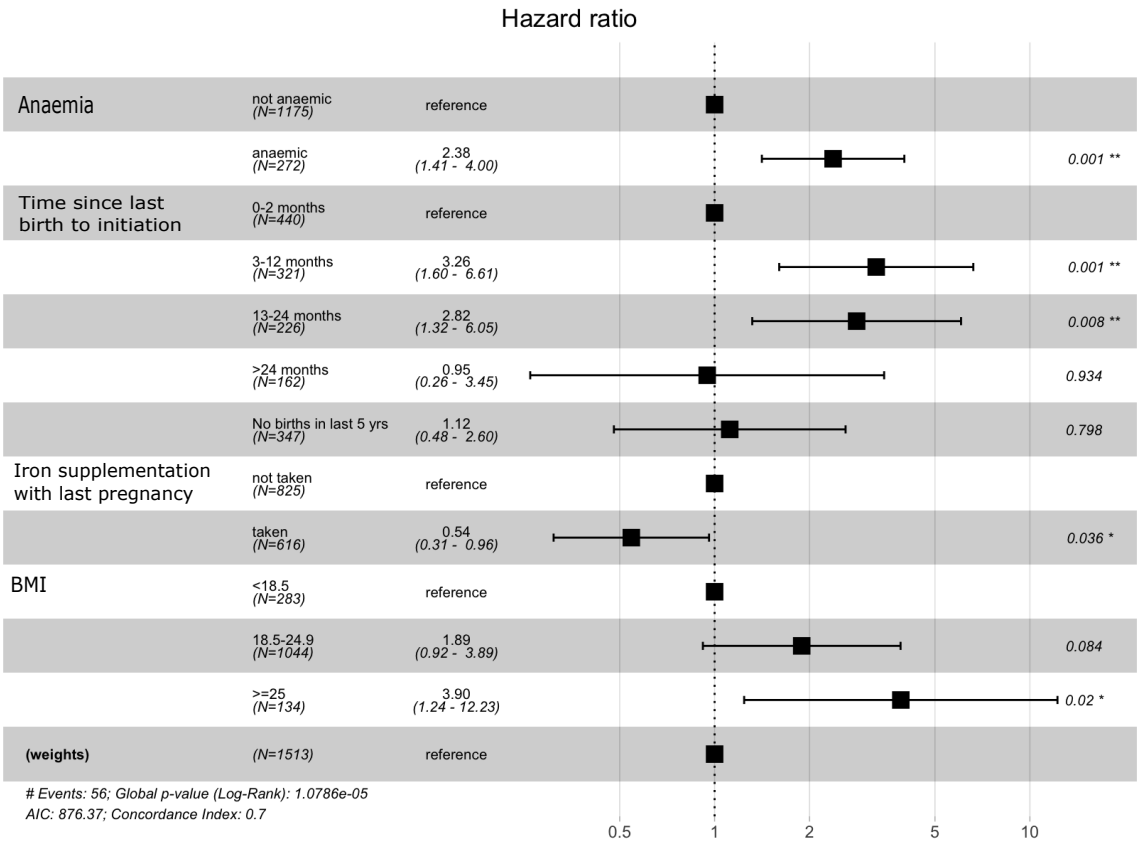

FIGURE 3 Adjusted hazard ratios and 95% CI for the association between each factor and risk of discontinuation due to other reasons (DOR)