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TREATMENT OF GENITAL MYCOPLASMA IN COLONIZED PREGNANT WOMEN IN LATE PREGNANCY IS ASSOCIATED WITH A LOWER RATE OF PREMATURE LABOUR AND NEONATAL COMPLICATIONS

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ABSTRACT

Mycoplasma hominis and *Ureaplasma* spp. may colonize the human genital tract and have been associated with adverse pregnancy outcomes such as preterm labour and

preterm premature rupture of membranes. However, as these bacteria can reside in the normal vaginal flora, there are controversies regarding their true role during pregnancy and thus the need to treat these organisms. We thus conducted a retrospective analysis to evaluate the treatment of genital mycoplasma in 5377 pregnant patients showing symptoms of potential obstetrical complications at 25-37 weeks gestation. Women presenting with symptoms were routinely screened by culture for the presence of these bacteria and treated with clindamycin when positive. Compared to uninfected untreated patients, women treated for genital mycoplasma demonstrated lower rate of premature labour. Indeed preterm birth rates were respectively 40.9% and 37.7% in *Ureaplasma* spp. and *M. hominis* colonized patients, compared to 44.1% in uncolonized women (*Ureaplasma* spp. p=0.024; *M. hominis* p=0.001). Moreover, a reduction of neonatal complication rates was observed, with 10.9% of newborns developing respiratory diseases in case of *Ureaplasma* spp. colonization and 5.9% in the presence of *M. hominis*, compared to 12.8% in the absence of those bacteria (*Ureaplasma* spp. p=0.050; *M. hominis* p<0.001). Microbiological screening of *Ureaplasma* spp. and/or *Mycoplasma hominis* and pre-emptive antibiotic therapy of symptomatic pregnant women in late pregnancy might thus represent a beneficial strategy to reduce premature labour and neonatal complications.

INTRODUCTION

Ureaplasma spp. and *Mycoplasma hominis* are members of the *Mycoplasmataceae* family, characterized by their lack of a cell wall and limited biosynthetic abilities. They are typically found in the urogenital tract of men and women and are therefore often referred to as

"genital mycoplasma" [1]. *Ureaplasma* spp. refer to both *U. urealyticum* (formely *U. urealyticum* biovar 2) and *U. parvum* (formely *U. urealytica* biovar 1), which have recently been separated into two different species.

The potential pathogenic role of these bacteria during pregnancy was recently reviewed [1]. Some studies have shown an association of vaginal colonization by *M. hominis* or *Ureaplasma* spp. with adverse pregnancy outcomes, such as preterm labour [2][3], preterm premature rupture of membranes (PPROM) [1] and chorioamnionitis [1]. Additionally, maternal infection can lead to major neonatal complications such as lung diseases, meningitis and septicaemia [4]. However, other studies failed to demonstrate a pathogenic role of these bacteria during pregnancy [1][5][6]. Thus, their exact role remains unclear and the benefits of screening and treatment strategies are still controversial.

In order to better address these issues, the present study aims to evaluate the influence of vaginal colonization by *M. hominis* and/or *Ureaplasma* spp. and subsequent treatment on pregnancy and neonatal outcomes.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION

This work is a retrospective study. Between 1998-2011, we collected vaginal samples from pregnant women attending the obstetrics department at University Hospital of Lausanne, Switzerland. Vaginal samples were collected from patients, between 25-37 weeks gestation who exhibited obstetrical signs and symptoms such as uterine contractions, abdominal pain, vaginal bleeding, suspicion of PPROM or cervical length shortening on transvaginal ultrasound (<25mm). These signs and symptoms may be associated with adverse

pregnancy outcomes, notably premature labour, PPROM or chorioamnionitis and therefore justify specific investigations. All samples were thus tested for the presence of *M. hominis* and *Ureaplasma* spp. by culture. Patients whose samples were positive to one or both bacteria were treated with clindamycin 150mg qid for 5 days. Demographic data, adverse pregnancy and neonatal outcomes among treated and untreated women were subsequently analysed, using our computerized obstetrical database (DIAMM, http://www.micro6.fr/) of prospectively collected data at the Maternity Hospital of the CHUV. The study was approved by the Ethical Committee of the University and Hospital, Lausanne, Switzerland (Protocol 46/14, date of approval 12th of February 2014).

SPECIMEN COLLECTION AND CULTURE

Vaginal swabs were taken using the Copan e-swab kit (Copan Diagnostics, Brescia, Italy). Specimens were placed on culture medium plates specific for *Ureaplasma* spp. and *M. hominis* (*A7 Mycoplasma agar*, BioMérieux, France). After 24-48h of incubation in a low-concentration oxygen atmosphere at 37°C, plates were analysed quantitatively by inverse microscopy. Positive cultures to *Ureaplasma* spp. and/or *M. hominis* were defined morphologically as previously described [1] and quantitative analysis was based on the number of colonies per field.

STATISTICAL ANALYSIS

Categorical variables were compared using the Pearson Chi-square test. Differences in the means of normally distributed continuous variables were tested by the Student's t-test and differences in medians by the Mann-Whitney test. Multivariable analyses were performed to

control for covariates. Multivariate logistic regressions were performed to identify factors independently associated with prematurity (birth <37 weeks of gestation). Multiple logistic regression (stepwise) models were developed, and odds ratios (OR) were used to evaluate risk factors associated with prematurity. A two tailed P value <0.05 was considered significant. Data were analysed using Stata 13 (Stata Corporation, College Station, TX).

RESULTS

Of the 5377 patients tested, 2259 (42%) had a positive culture for *Ureaplasma* spp. and/or *M. hominis*. Table 1 and 2 show the sociodemographic characteristics and associated outcomes of women with a positive swab culture for *Ureaplasma* spp. and *M. hominis,* respectively. Young age (p<0.001), nulliparity (p=0.009), obesity (p=0.001), ethnicity (p<0.001) and cigarette (p<0.001), alcohol (p=0.001) or drug (p<0.001) consumption were identified as risk factors for *Ureaplasma* spp. and/or *M. hominis* colonization during pregnancy in both univariate and multivariate analyses.

Of the 5377 patients tested, 2296 (42.7%) delivered prematurely (<37 weeks gestation). Preterm birth occurred less frequently in patients treated for genital mycoplasma (*Ureaplasma* spp. p=0.024; *M. hominis* p=0.001). Association between treatment and reduced rate of preterm labour remained significant even when adjusted for other known risk factors of premature labour, such as maternal age, cigarette smoking, alcohol and drug consumption, obesity and ethnicity. A multivariate logistic regression model associated with *M. hominis* colonization is shown in figure 1. No difference was observed in the rate of PPROM or mode of delivery. The interval between swab collection and delivery was

prolonged by 6 days for *Ureaplasma* spp. (74 versus 68 days, p=0.027) and 11 days for *M. hominis* (79 versus 68 days, p=0.008) compared to uninfected untreated patients. Duration of hospital stay was reduced for treated women (*Ureaplasma* spp. p=0.021; *M. hominis* p=0.017).

Early neonatal adaptation was similar between uninfected versus *Ureaplasma* spp. and *M. hominis* infected patients. However, neonates from treated women were less frequently admitted to the Neonatal Intensive Care Unit (NICU) (p<0.001) and had a shorter hospital stay (p<0.001). Additionally, significant decrease in acute respiratory complications was observed among neonates from treated women (*Ureaplasma* spp. p=0.050; *M. hominis* p<0.001) as compared to neonates from uninfected untreated women.

Patients treated for a co-infection by both *Ureaplasma* spp. and *M. hominis* exhibited similar reduction in preterm birth (Unadjusted OR 0.79; 95% CI 0.68-0.92; Adjusted OR 0.84; 95% CI 0.72-0.98), neonatal stay >7 days (Unadjusted OR 0.34; 95% CI 0.26-0.45; Adjusted OR 0.36; 95% CI 0.27-0.47), NICU admission (Unadjusted OR 0.12; 95% CI 0.08-0.20; Adjusted OR 0.13; 95% CI 0.08 0.21) and respiratory diseases (Unadjusted OR 0.41; 95% CI 0.30-0.55; Adjusted OR 0.42; 95% CI 0.31-0.57). Detailed data are shown in supplementary material.

DISCUSSION

In this study we focused on the effects of antimicrobial treatment of vaginal mycoplasma colonization on symptomatic pregnant women. We demonstrated a reduction of preterm birth rate in patients treated for genital mycoplasma compared to uninfected untreated

women. Moreover, we showed a striking reduction of neonatal complications in treated mothers. Neonates born from treated mothers had less respiratory complications and were less frequently admitted to the NICU compared with neonates from uninfected untreated women.

The prevalence of colonization was significant, with 42% of screened patients having a positive culture for either *Ureaplasma* spp. or *M. hominis*. *M. hominis* was detected less frequently than *Ureaplasma* spp. as previously reported [1][7][8]. Risk factors for colonization included young age, nulliparity, obesity, non-Caucasian origin as well as various drugs consumption.

We recently reviewed the implications of *Ureaplasma* spp. and *M. hominis* in adverse pregnancy outcomes [1]. Growing evidence suggests a role of cervicovaginal colonization as well as amniotic fluid infection with both pathogens in adverse pregnancy outcomes. *Ureaplasma* spp. and *M. hominis* are sensitive to macrolides, clindamycin, quinolones and tetracyclines. However, *Ureaplasma* spp. appear to be more susceptible to macrolides whereas *M. hominis* responds better to tetracyclines and quinolones. In the present study, clindamycin was used in patients positive for genital mycoplasma. A higher impact in term of prevention of preterm birth and adverse neonatal outcomes was identified for patients treated for *M. hominis* compared to *Ureaplasma* spp., which can be explained by greater antibiotic susceptibility of *M. hominis* [1].

The controversy regarding *Ureaplasma* spp. and *M. hominis* treatment in pregnancy has hindered any definitive conclusions regarding whether treatment for these mycoplasma affects pregnancy outcomes and neonatal health [1]. One report demonstrated the effectiveness of oral erythromycin in reducing second trimester spontaneous abortion in a

case of genital mycoplasma colonization. However, effects on premature labour were inconclusive [9]. In a case of premature labour at 27 weeks, which was associated with *U. urealyticum* colonization, Smorgick *et al*. observed that treatment with erythromycin, fluoroquinolones and clindamycin prolonged the pregnancy until 33 weeks, when spontaneous labour occurred. Cultures from the placenta were sterile but histopathological signs of chorioamnionitis were documented in placental samples [10]. Similarly, Romero *et al*. observed that treatment with erythromycin, clindamycin, ampicillin and gentamicin prolonged the pregnancy for 22 days, although spontaneous labour still occurred prematurely in a case where PPROM was associated with *Ureaplasma* spp. colonization [11]. Such observations were confirmed in a non-human primate model. Indeed, in *U. parvum* induced chorioamnionitis, intravenous azithromycin prolonged the pregnancy and prevented advanced foetal lung injury, despite the persistence of residual acute chorioamnionitis [12].

Hence, different hypothesis may explain why antimicrobial treatment of intra-amniotic infection with mycoplasma may be beneficial to the foetus. First, intra-amniotic infection may trigger an accelerated foetal lung maturation leading to a lower risk of respiratory distress after birth [13]. Moreover, antibiotic treatment of infected mothers may further improve neonatal outcomes by: 1) limiting intra-amniotic bacterial load and therefore reducing subsequent foetal inflammatory response and induced lung injury [12] and 2) prolonging pregnancy, thus reducing the risk of respiratory problems due to lung immaturity.

Limitations of our retrospective study include the lack of information on patient compliance. Another limitation of our study is the lack of information regarding previous

preterm labour. Additionally, *U. urealyticum* and *U. parvum* were not identified at the species level. Moreover, our study was made on a symptomatic population and thus at higher risk of adverse pregnancy outcomes as compared to asymptomatic women. This is confirmed by the high prevalence of premature labour in our study (42.7%) as compared to the general population, in which it only affects approximately 10% of pregnancies [14].

In addition, we did not investigate the effects of *Ureaplasma* spp. and *M. hominis* on pregnancy and neonatal outcomes, but instead analysed the impacts of their treatment. Therefore, our results might also be explained by the eradication of other pathogenic agents susceptible to clindamycin that were not detected in our study. Thus, for example, *Waddlia chondrophila* and *Parachlamydia acanthamoebae*, not detected on routine culture media, have been shown to be implicated in human adverse pregnancy outcomes [15][16][17] and are both sensitive to clindamycin and macrolides [18][19]. A similar, conclusion can be made for *C. trachomatis* [20][16][17] or the presence of bacterial vaginosis (BV) [21], which we did not evaluate. Our results might therefore be explained by the use of clindamycin in late pregnancy and not by the eradication of *Ureaplasma* spp, or *M. hominis* especially as we have no information on the clearance of the urogenital mycoplasma. Moreover, two recent meta-analyses on the efficacy of clindamycin in preventing preterm labour in cases of BV concluded to a reduction of the preterm birth rate when treatment was achieved in second trimester [22][23]. Additionally, a recent review in the Cochrane Library [24], concluded to a prolongation of pregnancy and reduction of a number of short term neonatal complications when antibiotics where giving in cases of PPROM. Clindamycin might be effective in reducing preterm labour either by eradicating pathogens or simply by reducing inflammation. However in a recent report, Diaz-Cueto showed that clindamycin was effective in reducing two important inflammation mediators, IL-1 and IL-6, but not the metalloproteinase 8 [25]. This could lead to cervical extracellular matrix degradation and

subsequent induction of premature labour. Thus, the authors concluded in an inefficacy to reduce preterm birth associated with BV. Despite such contradictory data that led to controversies in the field, the present work on more than 5000 patients strongly support the use of clindamycin when urogenital mycoplasma are detected in such situations.

In conclusion, we demonstrate the benefits of treating genital mycoplasma during pregnancy as it is associated with a lower rate of preterm birth and better neonatal outcomes. Therefore, we recommend screening of symptomatic pregnant women for which an adverse pregnancy outcome is suspected for the presence of these bacteria and prompt treatment when positive. Further investigations are needed to know whether routine treatment of all symptomatic patients with clindamycin might decrease the rate of adverse pregnancy outcomes even when neither colonized nor infected by genital mycoplasma by eradicating emerging pathogenic intracellular bacteria such as *Chlamydia*-related bacteria or other commonly adverse pregnancy-associated pathogens such as *C. trachomatis* or BV.

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TRANSPARENCY DECLARATION

The authors did not report any potential conflicts of interest.

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TABLE 1: Maternal and neonatal outcomes between patients with and without a positive vaginal swab culture to *Ureaplasma* spp..

	Negatives (n=3118) No.	%	***Ureaplasma* spp. (n=2221)** No.	%	**Unadjusted OR (95% CI) [a]**	**Adjusted OR [b] (95% CI)**
Maternal characteristics						
Age (years, mean ± SD)	31.8 ± 5.5		29.6 ± 5.9			
< 25	370	11.9%	516	23.2%	1.00	1.00
25-35	1846	59.2%	1298	58.4%	**0.51 (0.44-0.59)**	**0.54 (0.46-0.63)**
> 35	902	28.9%	407	18.3%	**0.33 (0.28-0.39)**	**0.35 (0.29-0.42)**
Nulliparous	1602	51.4%	1220	54.9%	**1.15 (1.03-1.28)**	1.02 (0.91-1.15)
BMI ≥ 30	641	20.6%	548	24.7%	**1.28 (1.12-1.45)**	**1.32 (1.16-1.51)**
Ethnicity						
Caucasian	2304	73.9%	1497	67.4%	1.00	1.00
Black	238	7.6%	270	12.2%	**1.21 (1.42-2.05)**	**1.68 (1.39-2.03)**
Others	576	18.5%	454	20.4%	**1.21 (1.05-1.39)**	**1.29 (1.12-1.49)**
Habits						
Alcohol	11	0.3%	24	1.1%	**2.86 (1.45-5.66)**	**2.42 (1.18-4.94)**
Smoking	260	8.3%	383	17.2%	**2.21 (1.87-2.61)**	**2.15 (1.80-2.56)**
Drugs	21	0.7%	44	2.0%	**2.64 (1.61-4.33)**	1.52 (0.90-2.60)
Pregnancy outcomes						
Gestational age (weeks, median)	37.3		38.0			
Preterm birth (< 37 weeks)	1376	44.1%	908	40.9%	**0.88 (0.79-0.98)**	**0.95 (0.85-1.07)***
PPROM	587	18.8%	414	18.6%	0.99 (0.86-1.14)	1.08 (0.93-1.24)
C-section	1343	43.1%	904	40.7%	0.91 (0.82-1.02)	1.03 (0.92-1.15)
Maternal stay ≥ 7 days	490	15.7%	300	13.5%	**0.83 (0.71-0 .97)**	0.93 (0.79-1.09)
Neonatal outcomes						
Apgar <7 at 5 minutes	318	10.2%	217	9.8%	0.96 (0.80-1.15)	1.03 (0.85-1.24)
Arterial pH <7.1	84	3.0%	56	2.8%	0.92 (0.65-1.29)	0.97 (0.68-1.37)
Admission in NICU	425	13.6%	235	10.6%	**0.75 (0.64-0.89)**	**0.80 (0.67-0.95)**
Neonatal stay ≥7 days	527	16.9%	290	13.1%	**0.74 (0.63-0.86)**	**0.80 (0.68-0.94)**
Weight						
SGA [c]	312	10.3%	266	12.0%	1.18 (0.99-1.40)	1.10 (0.93-1.32)
LGA [d]	414	13.3%	275	12.4%	0.93 (0.79-1.09)	0.97 (0.82-1.15)
Pathologies (any)	1365	43.8%	918	41.3%	0.91 (0.81-1.01)	0.96 (0.85-1.07)
Respiratory diseases [e]	398	12.8%	243	10.9%	**0.84 (0.71-0 .99)**	0.87 (0.73-1.03)
Infectious diseases [f]	157	5.0%	96	4.3%	0.85 (0.66-1.10)	0.91 (0.70-1.19)

Abbreviations: SD, standard deviation; BMI, body mass index; PPROM, preterm premature rupture of membranes; NICU, neonatal intensive care unit; SGA, small for gestational age; LGA, large for gestational age.

[a] Confidence interval ; those in bold are significant

[b] Adjusted for maternal age, BMI > 30, parity, ethnicity, smoking habits, as well as alcohol or drug consumption

[c] Birth weight <10th percentile

[d] Birth weigh >90th percentile

[e] Includes apnoea, respiratory distress, hyaline membrane diseases and respiratory tract infections

[f] Includes septicaemia, infections limited to one organ; excludes respiratory tract infections

* when adjusted only for parity, BMI, ethnicity and habits, preterm birth remains significant (OR = 0.88 ; 95% IC (0.79-0.99))

TABLE 2: Maternal and neonatal outcomes between patients with and without a positive vaginal swab culture to *M. hominis*.

	Negatives (n=3118) No.	%	*M. hominis* (n=912) No.	%	Unadjusted OR (95% CI) [a]	Adjusted OR [b] (95% CI)
Maternal characteristics						
Age (years, mean ± SD)	31.8 ± 5.5		29.7 ± 6.0			
< 25	370	11.9%	216	23.7%	1.00	1.00
25-35	1846	59.2%	527	57.8%	**0.63 (0.52-0.75)**	**0.70 (0.58-0.85)**
> 35	902	28.9%	169	18.5%	**0.46 (0.37-0.58)**	**0.53 (0.42-0.67)**
Nulliparous	1602	51.4%	529	58.0%	**1.28 (1.11-1.48)**	**1.21 (1.04-1.40)**
BMI ≥ 30	641	20.6%	222	24.3%	1.16 (0.98-1.37)	1.17 (0.99-1.39)
Ethnicity						
Caucasian	2304	73.9%	610	66.9%	1.00	1.00
Black	238	7.6%	104	11.4%	**1.33 (1.05-1.68)**	**1.34 (1.06-1.70)**
Others	576	18.5%	198	21.7%	**1.24 (1.04-1.49)**	**1.31 (1.10-1.57)**
Habits						
Alcohol	11	0.3%	8	0.9%	1.40 0(0.65-3.03)	1.23 (0.55-2.75)
Smoking	260	8.3%	165	18.1%	**1.79 (1.48-2.17)**	**1.75 (1.43-2.14)**
Drugs	21	0.7%	21	2.3%	**2.21 (1.32-3.70)**	**1.51 (0.88-2.59)**
Pregnancy outcomes						
Gestational age (weeks, median)	37.3		38.1			
Preterm birth (< 37 weeks)	1376	44.1%	344	37.7%	**0.78 (0.67-0.90)**	**0.82 (0.71-0.95)**
PPROM	587	18.8%	153	16.8%	0.85 (0.71-1.03)	0.90 (0.74-1.09)
C-section	1343	43.1%	365	40.0%	0.90 (0.78-1.05)	0.98 (0.85-1.14)
Maternal stay ≥ 7 days	490	15.7%	112	12.3%	**0.77 (0.62-0.95)**	**0.82 (0.66-1.01)**
Neonatal outcomes						
Apgar <7 at 5 minutes	318	10.2%	84	9.2%	0.90 (0.71-1.15)	0.94 (0.73-1.20)
Arterial pH <7.1	84	3.0%	25	3.0%	1.04 (0.67-1.60)	1.07 (0.69 - 1.66)
Admission in NICU	425	13.6%	22	2.4%	**0.15 (0.10-0 .23)**	**0.15 (0.10 - 0.24)**
Neonatal stay ≥7 days	527	16.9%	63	6.9%	**0.36 (0.28-0.47)**	**0.39 (0.29 - 0.50)**
Weight						
SGA [c]	312	10.3%	102	11.2%	1.02 (0.82-1.28)	0.95 (0.76-1.20)
LGA [d]	414	13.3%	108	11.9%	0.89 (0.72-1.11)	0.94 (0.75-1.17)
Pathologies (any)	1365	43.8%	384	42.1%	0.97 (0.84-1.12)	1.00 (0.87 - 1.17)
Respiratory diseases [e]	398	12.8%	54	5.9%	**0.41 (0.31-0.55)**	**0.42 (0.32 - 0.57)**
Infectious diseases [f]	157	5.0%	8	0.9%	**0.15 (0.08-0.30)**	**0.16 (0.08 - 0.33)**

Abbreviations: SD, standard deviation; BMI, body mass index; PPROM, preterm premature rupture of membranes; NICU, neonatal intensive care unit; SGA, small for gestational age; LGA, large for gestational age.

[a] Confidence interval ; those in bold are significant

[b] Adjusted for maternal age, BMI > 30, parity, ethnicity, smoking habits, as well as alcohol or drug consumption

[c] Birth weight <10th percentile

[d] Birth weigh >90th percentile

[e] Includes apnoea, respiratory distress, hyaline membrane diseases and respiratory tract infections

[f] Includes septicaemia, infections limited to one organ; excludes respiratory tract infections

FIGURE 1: Multivariate logistic regression model to identify independent risk factors of premature birth.

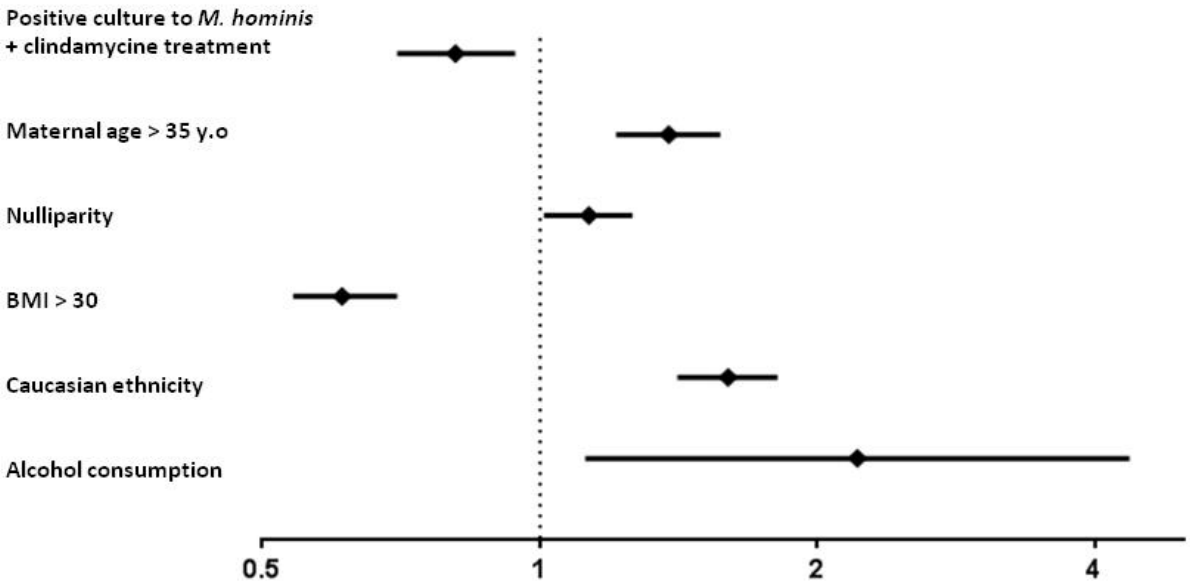

FIGURE 1: Multivariate logistic regression model to identify risk factors of premature birth.

This figure represents the adjusted OR, with corresponding 95% confidence interval, in a logarithmic scale

Abbreviations: y.o , years old