Article

Maternal ethnicity as risk factor for miscarriage: evidence from a six-year period cohort in a university setting

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Abstract: In last decades, growing migration flows have modified the obstetric clinical care, requiring specific attention by health care systems. The aim was to describe the phenomenon focusing on miscarriage (pregnancy loss at <20 weeks). Patients admitted for care at miscarriage in a six-year period (2012-17) were revised. Miscarriage rates in all ethnic groups, dichotomized in early (within the first 12 weeks of gestation) and late (at <20 weeks) pregnancy loss. Associations between women's characteristics (age, parity, inter-pregnancy interval (IPI)) were explored to elucidate any differences. A total of 1,940 patients were included, segregated in early (n=1,769, 91.2%) and late (n=171, 8.8%) pregnancy losses. Caucasian ethnicity was the most common (87.9%), leaving the minority groups to 12.1%. Maternal age was higher among Caucasians women than other subgroups, in contrast to Asiatic patients. Nulliparity was observed in 1,045 (53.9%) patient, more widespread among Caucasian and Maghrebins. A positive obstetric history counting at least one miscarriage was frequent, ranging from 22.2% to 75%, in particular among Asiatic women, while the recurrence in Caucasians. In Afro-Carribeans the most relevant rate of late miscarriage was found. By multiple regression modelling, maternal age, nulliparity and Afro-Carribean were identified as determinants. Maternal ethnicity should be considered in the management of pregnancy losses in combination with already well-defined risk factors, including age at miscarriare and nulliparity.

Keywords: miscarriage, fetal loss, risk factor, ethnicity, maternal race.

1. Introduction

Despite years of research, miscarriage, mostly if recurrent, remains a clinical challenge. Establishment of early pregnancy is the result of complex biochemical interactions between the decidua and blastocyst. As consequence, any alteration in this chemical dialogue has the potential to result in adverse pregnancy outcomes, including spontaneous abortion. Sporadic miscarriage, as the

most common complication of pregnancy, can be determined by multifactorial and complex pathogenesis. [1]. Approximately 10%–15% of clinically identified pregnancies end in recognized miscarriage, defined as a pregnancy an early and late loss before completion of 13 and 20 weeks' gestation, respectively [2]. In depth, more than a third of all conceptions that can be identified hormonally may end in loss when taking into account unrecognized pregnancies [3]. Few biological, behavioral, or socioeconomic factors have been definitively associated with risk of miscarriage [4-6]. An embryo chromosomal error is responsible for 50-60% of overall cases [7], while, up to 30-50% remains an enigma [8]. Among other contributing factors, maternal disease preexisting to the pregnancy, preconception obesity, biological factors and environmental toxins in reproduction can play a role in the pregnancy loss [9].

Over the years, rising migration flows have modified the clinical scenario in hospital settings. Also, the research approach has been influenced by the ethnic component not only in the construction of predictive models for selecting among all patients those at higher risk to develop complications, but also in the growth of a personalized medicine. In obstetrics, the role of maternal origin is well-established in several complications (i.e., preeclampsia, preterm deliveries, fetal growth restriction, and gestational diabetes). In contrast, some studies incorporating race into multivariable models of miscarriage risk conclude with opposite findings, ranging from a doubled risk of miscarriage for Blacks compared with other ethnic groups [10], to no association between race and miscarriage risk [11-13]. A recent survey designed to describe the spontaneous abortion trend among Italian based on ISTAT database found that immigrant miscarriage rates resulted higher than Italian ones [14]. Of interest, the effect of maternal age on the miscarriage incidence resulted different, with increasing of age more associated with Italian women and an opposite trend for immigrant patients [14]. To complete, the Authors reported a miscarriage incidence significantly dissimilar according to the maternal educational level, providing a socioeconomic explanation in addition to the biological or genetic factors [14]. However, the study lacks in specifying the impact of ethnicity on miscarriage in Italy.

To the best of our knowledge, no previous studies have been addressed to explore the role of maternal ethnicity in early and late pregnancy loss. In agreement, the aim of the study was twice: firstly, to report the miscarriage rates in all ethnic groups, dichotomized in early (within the first 12 6/7 weeks of gestation) and late (at <20 weeks) pregnancy loss; secondly, to explore associations between women's characteristics, such as age, parity, inter-pregnancy interval (IPI) between study groups.

2. Materials and Methods

2.1 Study population

Between January 2012 to December 2017 all women with a diagnosis of miscarriage and admitted at the Department of Obstetrics and Gynecology, Fondazione Policlinico Universitario 'A. Gemelli' IRCCS, Rome, Italy, were included in the analysis. The hospital is a tertiary referral center with an average of 350 surgical treatment for miscarriage (dilation and curettage, D&C) per annum at the study time (2012-2017). The local Institutional Review Board approved the research project (IRB 16_10_2017). Due to the nature (retrospective) of the study, patients signed any consent.

2.2 Collection of resource use data

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From the local D&C Registry all information pertaing maternal characteristics, including place and date of birth, age at D&C, nationality, marital status (married/unmarried), parity, previous miscarriages, inter-miscarriage interval, miscarriage-to-delivery interval, and potential etiology were collected. All patients were categorized according to the ethnicorigin (Caucasian, Latin-American, Afro-Caribbean, Asian, and Maghrebian), and gestational age at miscarriage (early versus late).

2.3 Clinical management

At admission, all patients were formally assessed to ensure that the correct clinical management had been followed, according to local protocols. An ultrasound scan was performed in order to confirm uterine localization of miscarriage requiring D&C. A consent form giving permission to realize the therapeutic procedure was signed by all patients. In a preoperative step, the maternal blood assessment was carried out, including complete blood count, basic tests on coagulative disorders, blood typing and Rh testing, and ongoing infection miscarriage-related. Vaginal exploration was achieved to determine size and position of uterus and cervical dilation. In absence of any dilation and haemodynamic stability, a pharmacological treatment based on intravaginal prostaglandin (Gemeprost, 1mg, to be repeated every 3 hours for late miscarriage until a maximun of five doses) was chosen, followed by D&C 2-3-hours later. Prompt surgical uterine evacuation was the choice treatment if the patient was unstable due to massive bleeding or septic abortion. Conversely, expectant or medical management was preferred in selected patients, with a completed spontaneous abortion.

2.4 Definitions and outcome measures

Early and late pregnancy loss was defined as occurred within the first 12 weeks of gestation and at <20 weeks, respectively [2]. IPI was divided into inter-miscarriage interval (IMI) and miscarriage-to-delivery interval (IMDI), calculating the period between two miscarriage events and between previous pregnancy and miscarriage, respectively.

The primary outcome was to define the miscarriage rate in all ethnic groups, distinguishing early versus late pregnancy loss. The secondary outcomes explored the association between women's characteristics, such as age, ethnicity, parity, inter-pregnancy interval (IPI) between study groups.

2.5 Statistical analysis

Normal distributions were assured by the Shapiro-Wilk test. The Student's t-test for independent samples, the Mann-Whitney-U test, Pearson's chi-square or exact Fisher's tests were used to analyze collected data, as appropriate. A stepwise logistic regression to estimate odd risk (OR) and 95% confidence intervals (CI) for the associations between onset at miscarriage and maternal characteristics.

All tests were two-sided, and p-values lower than 0.05 were established statistically significant. IBM SPSS 23.0 (Armonk, NY, USA) and R version 2.15.1 (The R Foundation for Statistical Computing) with package version 1.7.2 software were used for statistical analyses.

2.6 Patients and Public Involvement

Patients and public were not involved in the development of the research question or outcome measures, design of the study, recruitment process, conduct of the study, or creation of this

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manuscript. The dissemination of the results will be performed also by the Institutional website (www.policlinicogemelli.it).

3. Results

In the six-year period study, 1,940 women referred to the local Department of Obstetrics and Gynecology for clinical assistance at miscarriage were included in the analysis. The overall and segregated distribution per annum in early (n=1,769, 91.2%) and late (n=171, 8.8%) pregnancy losses are displayed in Figure 1.

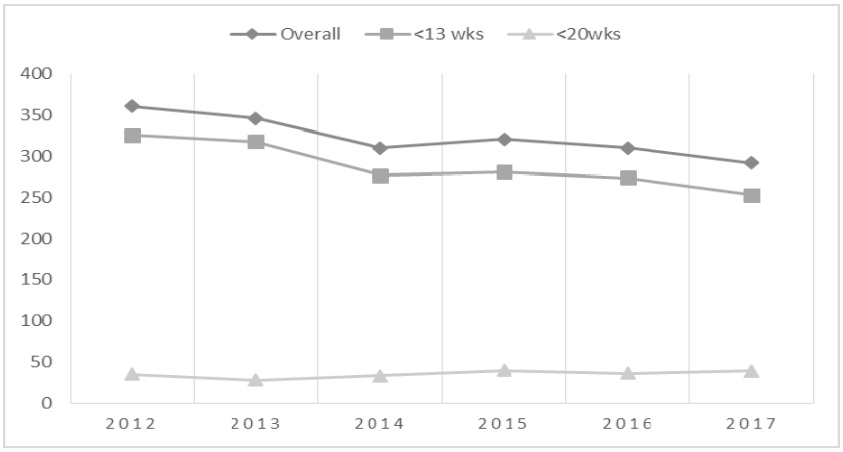

Figure 1. Distribution of miscarriage in women referred for assistance in the six-year period, distinguished in overall, early and late pregnancy losses.

All of them were categorized in agreement with the maternal ethnic origin criterion, as depicted in Figure 2.

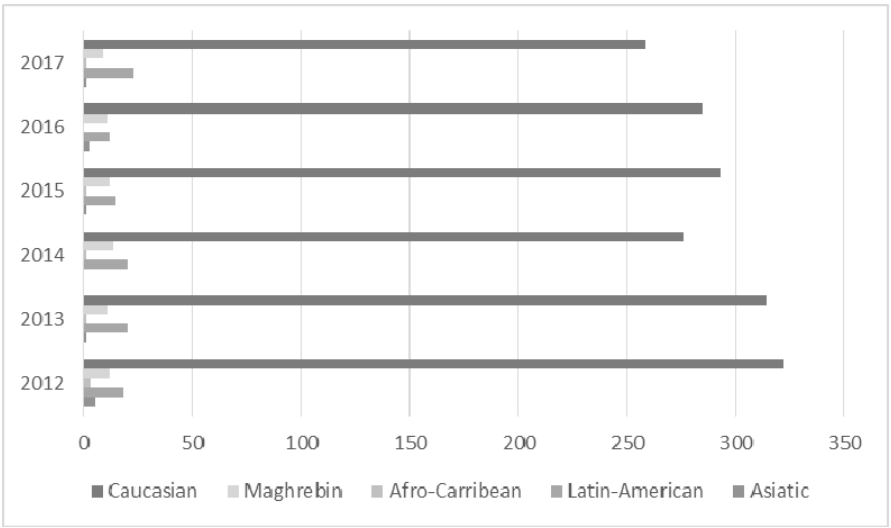

Figure 2. Distribution of miscarriage in women referred for assistance in the six-year period according to the maternal racial criterion.

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Caucasian ethnicity was the most common (87.9%), leaving the minority groups to 12.1%. Demographic characteristics and obstetric history of overall population and subgroups were detailed in Table 1 and Table 2, respectively.

Tab. 1. Demographic characteristics and obstetric history of the study population, expressed as mean (SD) or n (%), as appropriate.

	Overall (n=1,940)
Maternal age	35.7 (5.6)
Ethnicity	
- **Caucasian**	1705 (87.9)
- **Asian**	68 (3.5)
- **Latin-America**	111 (5.7)
- **Afro-Caribbean**	18 (0.9)
- **Maghrebin**	38 (2)
Obstetric history	
- **Nulliparity**	1,045 (53.9)
- **One previous miscarriage**	478 (24.6)
- **Two previous miscarriages**	195 (10.1)
- **Three previous miscarriages**	71 (3.7)
- **Four or more miscarriages**	22 (1.2)
- **One previous delivery**	632 (32.6)
- **Two previous deliveries**	187 (9.6)
- **Three previous deliveries**	50 (2.6)
- **Four or more deliveries**	25 (1.3)
Inter miscarriage interval	
- **<one year**	89 (4.6)
- **one year**	222 (11.4)
- **two years**	121 (6.2)
- **three years**	71 (3.7)
- **>4 years***	499 (74.1)
Miscarriage-to-delivery interval	
- **<one year**	19 (1)
- **one year**	113 (5.8)
- **two years**	150 (7.7)
- **> 3 years**	145 (7.5)
- **>4 years****	580 (78)

* Maximum interval until 27yrs. ** Maximum interval until 23yrs

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Tab. 2. Obstetric history of the study population segregated into maternal ethnic criterion, expressed as mean (SD) or n (%), as appropriate.

	Caucasian (n=1,705)	Asiatic (n=68)	Latin-America (n=111)	Afro-Caribbean (n=18)	Maghrebin (n=38)
Maternal age at miscarriage	35.8 (5.4)	32.8 (5.2)	34.9 (7.2)	34.6 (5.5)	34.7 (6.7)
Obstetric history					
- **Nulliparity**	941 (55.2)	30 (44.1)	43 (38.7)	7 (38.9)	24 (63.2)
- **1 previous miscarriage**	409 (24)	51 (75)	39 (35.1)	4 (22.2)	17 (44.7)
- **2 previous miscarriages**	173 (10.1)	12 (17.6)	22 (19.8)	3 (16.7)	15 (39.5)
- **3 previous miscarriages**	64 (3.8)	3 (4.4)	6 (5.4)	2 (11.1)	3 (7.9)
- **4 or more miscarriages**	18 (10.6)	2 (2.9)	1 (0.9)	1 (5.6)	1 (2.6)
- **1 previous delivery**	557 (32.7)	25 (36.8)	39 (35.1)	5 (27.8)	6 (15.8)
- **2 previous deliveries**	145 (8.5)	10 (14.7)	22 (19.8)	5 (27.8)	5 (13.2)
- **3 previous deliveries**	37 (2.2)	3 (4.4)	6 (5.4)	2 (11.1)	3 (7.9)
- **4 or more deliveries**	15 (1.5)	0 (0)	1 (0.9)	0 (0)	0 (0)
Inter miscarriage interval					
- **<1 year**	80 (4.7)	2 (2.9)	3 (2.7)	2 (11.1)	2 (5.3)
- **1 year**	198 (11.6)	4 (5.8)	10 (19)	4 (22.2)	6 (15.8)
- **2 years**	109 (6.4)	1 (1.5)	6 (5.4)	1 (5.6)	5 (13.2)
- **3 years**	63 (3.7)	1 (1.5)	7 (6.3)	1 (5.6)	2 (5.3)
- **>4 years***	197 (11.6)	8 (11.8)	28 (25.2)	0 (0)	21 (55.3)
Delivery-to-miscarriage interval					
- **<1 year**	14 (0.8)	2 (2.9)	3 (2.7)	1 (5.6)	2 (5.3)
- **1 year**	105 (6.2)	2 (2.9)	4 (3.6)	1 (5.6)	2 (5.3)
- **2 years**	134 (7.9)	8 (11.8)	5 (4.5)	1 (5.6)	1 (2.6)
- **3 years**	128 (7.5)	5 (7.4)	10 (9)	2 (11.1)	4 (10.5)
- **>4 years****	494 (29)	36 (52.9)	67 (60.4)	10 (55.6)	14 (36.8)

* Maximum interval until 27yrs. ** Maximum interval until 23yrs

Of interest, maternal age was higher among Caucasians women than other subgroups, in contrast to Asiatic patients. A total of 1,045 (53.9%) patient were nulliparous, with prevalence among Caucasian and Maghrebin. A positive obstetric history of one miscarriage was frequent, ranging from 22.2% to 75%, more prominent among Asiatic women. The recurrence was more evident in Caucasians. One or more deliveries have been accounted among ethnic groups showing similar distribution, with the

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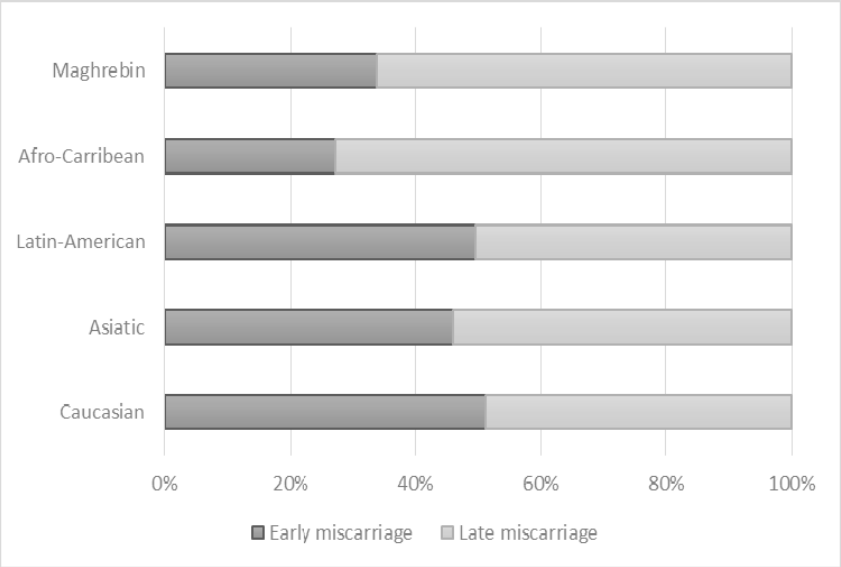
exception of Maghrebin patients. A one-year period of IMI was common among all women with at least two pregnancies losses, as well as a mean for IMDI.

Figure 3 illustrates the distribution of miscarriage rates according to the maternal ethnic criterion and expressed as onset at pregnancy loss.

Figure 3. Distribution of miscarriage in women referred for assistance in the six-year period according to the maternal ethnic criterion crossed with the onset at miscarriage.



The most relevant rate of late miscarriage was found among Afro-Caribbean women.

Finally, by multiple regression modelling, the association between maternal variables and miscarriage was explored (Table 3).

Table 3. Association of ethnicity and complications in miscarriage.

	Early miscarriage OR [95% CI]	**P-value**
Maternal age	0.968 [0.941-0.996]	0.024
Nulliparity	0.718 [0.518-0.995]	0.047
Caucasian	0.501 [0.205-1.222]	0.129
Asiatic	0.734 [0.407-1.323]	0.304
Latin-America	0.757 [0.523-1.098]	0.143
Maghrebin	0.722 [0.513-1.076]	0.156
Afro-Caribbean	1.090 [1.005-1.554]	0.024

OR: odd ratio, CI: confidence interval.

Age at miscarriage, nulliparity and Afro-Caribbean were identified as determinants in our setting.

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4. Discussion

The study shows the role played by maternal ethnic origin in a miscarriage scenario, confirming not only in age at pregnancy loss and nulliparity as determinants in spontaneous abortion, but also that Afro-Caribbean ethnicity was more likely than other ethnic groups to experience a pregnancy loss. For them, the risk increases in late-onset of miscarriage.

In medical literature, a growing body of evidence attempt to explain etiology miscarriage-related, without however unicity in the clarification of underlying biological mechanisms and concluding in a multifactorial disease. Firstly, the role of chromosomal abnormalities have been documented in at least half of all pregnancy losses occurring in the first trimester [7,17]. Secondly, a failure of trophoblast tissue to block the spiral arteries reduces the oxygen environment needed for organogenesis and failure of a timely luteal-placental shift resulting in failure to maintain adequate progesterone support [18]. Thirdly, the remodeling of the spiral arteries to allow adequate maternal blood flow for fetal development occurs toward the end of the first trimester. This scenario could explain the elevated risk that we observed in Afro-Caribbean women and support investigations focused on maternal race in the contribution of obstetric disease.

In literature, previous studies have been delivered considering race as a confounder in assessing miscarriage risk [19,20] and examining it as a main effect [13]. This evidence agree in acknowledgment ethnicity as an independent factor in assessing miscarriage risk. Our data are in line with the growing body of the research findings focused on maternal ethnicity in the assessment of the risk of diseases in pregnancy. More in-depth and in contrast to other complications that can occur across the trimesters, spontaneous abortion requires careful assessment of gestational time at study entry. Women enrolled later will have less opportunity for a miscarriage to be managed than women who enter very early in pregnancy [13]. This issue is supported by previous collected data on very early gestational weeks, conclusive for a progressive increase in miscarriage risk by week of gestation [20].

A supplementary information from our study is related to maternal characteristics, such as age and parity. As know, miscarriage is a common pregnancy outcome and more likely to happen among women aged 35 years and older. It is due to fetal abnormalities and chromosomal abnormality linked to mutation by rising maternal age, or worse in-utero conditions [21]. In our setting, this was manifest among Caucasian women. We could speculate that culture, belief and the social role of women in the different ethnic groups influence the timing in the family planning in younger age classes, with significant benefits in terms of reduced adverse obstetric outcomes. At same time, nulliparity has found as potential determinant in logistic regression modelling. This finding was in line with previous evidence, conclusive for higher risk for antepartum, intrapartum, and neonatal complications than multiparous women. Nevertheless, these risks, for the most part, are manageable in the context of modern obstetrics [22].

Of interest, the analysis performed according the length of obstetric events, i.e. IMI and IMPI. We found that one year period of miscarriage interval was common among all women with at least two pregnancies losses, as well as a mean for IMPDI. In 541 women, Sundermann et al. reported an association between the IPI after pregnancy loss of less than 3 months and lowest risk of subsequent miscarriage, proposing a suitable counseling woman to delay conception to reduce risk of miscarriage [23].

In terms of the generalisability, our research findings can be applied to settings other than in which we obtained them. Indeed, moving from the internal validation able to describe the true state of medical activities within its own setting, the external validation is conceivable because the management of multiethnic patients with one or more miscarriage is wide-reaching.

The present study presents both strengths and limitations. This is the first investigation designed to explore the miscarriage rates distinguishing between early versus late onset. Additionally, the choice of the maternal race criterion endorses budding evidence on this matter in obstetrics. Finally, the analysis dichotomized into IMI and IMDP represent an enrichment in the characterization of the miscarriage topic. Conversely, we acknowledge that the retrospective nature could be considered as a true study limitation, as well as the missed inclusion of additional variables in the construction of the logistic regression modelling.

5. Conclusions

Maternal ethnicity should be considered in the management of pregnancy losses in combination with already well-defined risk factors, including age at miscarriare and nulliparity. The elevated risk of fetal loss in some selected ethnic groups should address the clinical practitioners to perform target counseling and prompt management in early stage of pregnancy in order to preserve the starting pregnancy.

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