

# Universal versus selective screening for the detection, control and prognosis of gestational diabetes mellitus in Argentina

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**Abstract** In all, 1,702 unselected pregnant women from the city of La Plata were tested for gestational diabetes mellitus (GDM) and evaluated to determine GDM prevalence and risk factors. In women with GDM, we evaluated compliance with guidelines for GDM management, and perinatal complications attributable to GDM. GDM prevalence was 5.8%, and its risk factors were pre-gestational obesity, previous hyperglycaemia, age > 30 years, previous GDM (and its surrogate markers). In primi-gravida (PG) subjects, GDM was equally prevalent in the presence

(4.2%) or absence (4.0%) of risk factors. In multi-gravida (MG) women, although risk factors doubled the prevalence of GDM (8.6%), in the absence of risk factors GDM prevalence was similar to that of PG women (3.9%). Half of all women with GDM received inadequate post-diagnosis obstetric control, and this induced a fourfold increase in infant perinatal complications. In conclusion, all non-hyperglycaemic 24–28-week pregnant women should be tested for GDM, although particular attention must be paid to MG women with risk factors.

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## Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity, which begins or is recognized for the first time in the index pregnancy [1]. Several factors which increase the risk for GDM have been identified pre-gestational obesity, maternal age > 30 years, belonging to a high risk ethnic group, a family history of diabetes mellitus, GDM in previous pregnancies and its surrogate markers: previous foetal macrosomia, previous perinatal infant mortality, third trimester hypertension. However, the relative importance of these risk factors is dependent on the population under study [2–4]. Untreated (or inadequately treated) GDM significantly increases both maternal perinatal morbidity, and infant perinatal morbidity and mortality [4, 5], supporting its timely detection. Since in most cases of GDM there are no overt clinical symptoms or fasting hyperglycaemia, diagnosis normally depends on its laboratory

screening with a standardized 1- or 2-step oral glucose tolerance test (OGTT).

There is an ongoing discussion to determine whether screening for GDM with an OGTT in non-hyperglycaemic pregnant women should be universal (i.e. testing all pregnancies) or selective (i.e. only testing pregnant women with risk factors for GDM) [6, 7]. The American Diabetes Association, the 4th International Workshop-Conference of GDM, and the Italian Association of Diabetologists all recommend selective screening [1, 8, 9]. However, the results of several recent studies indicate that in certain populations (e.g. Italian and Spanish) universal screening for GDM could be more adequate and cost-effective [6, 10, 11].

In Argentina, in which well over two-thirds of the general population is of Italian and/or Spanish origin, the prevalence of GDM has been found to range between 1.4 and 5% of all pregnancies [12]. In addition, investigators have reported that in Argentina untreated GDM is associated with a 20-fold increase in perinatal infant mortality: 15% in untreated versus 0.7% in treated GDM [13]. In general, Argentine obstetricians only test for GDM (with a 1-step diagnostic OGTT) in non-hyperglycaemic pregnant women who have one or more risk factors for this condition. This approach is based on the aforementioned international recommendations [1, 8, 9], and on the supposition that the prevalence of GDM in Argentine risk factor-free third trimester pregnant women is negligible, although this has not been investigated [14]. However, if this supposition were proven to be wrong, universal screening for GDM would have to be recommended.

An alternative approach could be to stratify pregnant women with a surrogate marker for established GDM risk factors, such as parity. As parity increases, an accumulation of various risk factors for GDM can be reasonably expected (such as age, obesity and an age-related decrease in insulin secretion and/or action). Other authors have previously related parity to prevalence of GDM in pregnant women of diverse ethnic backgrounds [15–17]. According to this alternative approach, each group [e.g. primi-gravida (PG) and multi-gravida (MG) women] could then be individually analysed to determine the prevalence of GDM from the presence or absence of risk factors, and thus the most appropriate strategy for GDM screening be evaluated for each group.

The objective of this study was to evaluate the usefulness of selective screening for the detection of GDM in the city of La Plata, Argentina, as well as the ability of the health care system to provide adequate post-diagnosis control of GDM and reduction of its perinatal complications. To this effect, we estimated the prevalence and risk factors for GDM in unselected women who controlled their

pregnancy in primary health care centres of the city of La Plata. In the case of pregnancies complicated by GDM, we also studied: (a) compliance with current national guidelines for the post-diagnosis management of GDM [13, 18]; and (b) frequency of GDM-associated perinatal maternal and/or infant complications.

## Subjects, materials and methods

### Ethical considerations

This study was approved by the Regional Committee for Bioethics and Clinical Investigation of the Buenos Aires Province Ministry of Health. Informed consent of participants was not necessary, since GDM testing forms part of the recommended pre-natal evaluation of pregnant women.

### Subjects, GDM testing and risk factor analysis

Pregnant women who were in 24–28 weeks of gestation attended any of the 23 primary health care centres in the city of La Plata for their antenatal control. They were consecutively recruited by their attending obstetricians into the study, and referred to a local reference laboratory for detection of GDM. Participating women were unselected (i.e. they entered the study independently of the presence or absence of previously described risk factors for GDM), and thus 1,702 subjects were screened for GDM according to the recommendations of the Argentine Diabetes Association [13]. Briefly, non-hyperglycaemic 24–28 gestation-week subjects [fasting plasma glucose (FPG) < 5.8 mmol/L] were submitted to an OGTT with a 75 g glucose oral load, and a 2-h post-load plasma glucose value ≥ 7.8 mmol/L was considered diagnostic for GDM. Hyperglycaemic subjects (FPG ≥ 5.8 mmol/L) were given an appointment for the following week and retested (FPG, plus OGTT if necessary) to determine their status (two elevated FPG values were also considered diagnostic for GDM).

During their testing for GDM, all participating subjects were interviewed in order to complete a questionnaire which included: age; week of gestation; weight (present and pre-gestational); height; first-degree relatives with diabetes mellitus; ethnic background (up to three generations); previous hyperglycaemia; previous pregnancies and, if so, previous GDM, macrosomia, infant perinatal mortality and/or third trimester hypertension. After testing for GDM, results for OGTT and/or FPG were also included in the questionnaire. All questionnaires were recorded on a computer, and data analysis for GDM prevalence and risk factors was performed with the Program of Statistics in Public Health Epi-Info 6.01.

## Follow-up of pregnancies complicated by GDM

In the case of subjects who tested positive for GDM, a postnatal analysis of the maternal and infant clinical histories was performed, in order to evaluate: (a) compliance with national guidelines for the post-diagnosis management of GDM [13, 18] (full compliance from GDM diagnosis to delivery was considered adequate control, while any degree of non-compliance was considered inadequate), and (b) possible perinatal maternal and/or infant complications attributable to GDM [4, 5]. National guidelines for the management of GDM have been outlined in Table 1, and are in turn based on recommendations proposed by various international diabetes associations.

### Statistical analysis

Gestational diabetes mellitus prevalence was calculated with a 95% confidence interval. Chi-square test was used for association between risk factors and GDM, and  $P < 0.05$  was considered significant. For each risk factor associated with GDM, odds ratio (OR) was calculated with a 95% confidence interval. Logistic regression models were

**Table 1** Summary of guidelines for the management of GDM recommended by the Argentine Diabetes Association [13, 18]

Management of all patients with GDM must be performed by an interdisciplinary team with fluid communication, which as a minimum should include an Obstetrician, a Diabetologist and a Neonatologist, according to the following guidelines

- (a) Diabetological education: if the patient has no prior diabetological education, it should be performed during a brief post-diagnosis hospitalization period, although it may also be performed in an ambulatory environment
- (b) Frequency of controls: every 15 days until the 30th week of gestation, then on a weekly basis until hospitalization for delivery (unless the patient presents a concurrent pathology that requires a greater frequency of controls)
- (c) Clinical examination must include physical examination, evaluation of nutritional status, body weight chart, BMI, evaluation of peripheral oedema, blood pressure
- (d) Glycaemic auto-monitoring: frequency and timing of monitoring depends on the severity of metabolic alterations
  - (d-1) If at diagnosis fasting glycaemia is normal, auto-monitoring should be performed before breakfast, 2 h before lunch and 2 h before dinner
  - (d-2) If at diagnosis the patient presents fasting hyperglycaemia, auto-monitoring should be performed before breakfast, before lunch, before mid-afternoon snack and 2 h before dinner
- (e) Daily ketonuria auto-monitoring before breakfast
- (f) Complete biochemical and haematological profiles. Glycated haemoglobin at diagnosis and every 6–8 weeks, or fructosamine at diagnosis and every 3 weeks
- (g) Routine obstetric examinations
- (h) Cardiologic evaluation

adjusted to evaluate the possible relationship between risk factors and probability for GDM. Mann–Whitney test was used to compare continuous variables.

## Results

Subject characteristics: prevalence and risk factors for GDM

Age and pre-gestational body mass index (BMI, kg/m<sup>2</sup>) were recorded for all 1,702 participants, which included 602 nulliparous or PG subjects and 1,100 multiparous or MG women. Results are shown in Table 2. As can be seen, MG subjects were older and had a greater BMI than PG subjects.

Of the 1,702, 24–28-week pregnant women who participated in this study, 99 tested positive for GDM, 21 being diagnosed by fasting hyperglycaemia and 78 by a pathological OGTT (with normal FPG). We found no difference in age, pre-gestational BMI or parity between women with GDM detected by fasting hyperglycaemia or by pathological OGTT (data not shown). However, 41% of women diagnosed by fasting hyperglycaemia referred to previous hyperglycaemia and/or previous GDM, as opposed to only 14% of women detected by a pathological OGTT. Prevalence of GDM was determined for all participants, for PG subjects and for MG subjects (Table 2). We found a significantly greater prevalence of GDM in MG than in PG subjects.

We also determined the risk factors for GDM (and their OR) in all participants, in PG and in MG (Table 3). When a

**Table 2** Age, pre-gestational BMI and prevalence of GDM in 24–28-week pregnant women of La Plata

Parameter under study (subject group)	Mean	95% Confidence interval	Range
Age (years)			
All participants	24.8	±6.3	13–45
Primi-gravida	20.5	±4.0	13–39
Multi-gravida	27.1*	±6.1	15–45
BMI (kg/m <sup>2</sup> )			
All participants	23.4	±4.6	14.7–44.8
Primi-gravida	22.5	±3.8	14.7–41.5
Multi-gravida	23.9*	±4.9	14.7–44.8
Prevalence of GDM (%)			
All participants	5.8	4.7–6.9	–
Primi-gravida	4.3	2.7–5.9	–
Multi-gravida	6.6**	5.2–8.1	–

\*  $P < 0.0001$  versus primi-gravida

\*\*  $P < 0.05$  versus primi-gravida

**Table 3** Risk factors for GDM in 24–28-week pregnant women of La Plata

Risk factor (group under study)	Odds ratio (OR)	95% Confidence interval for OR	Statistical significance
Previous hyperglycaemia			
All participants	5.56	[3.14; 9.84]	<i>P</i> < 0.0001
Primi-gravida	2.80	—	NS
Multi-gravida	5.56	[3.03; 10.23]	<i>P</i> < 0.0001
Age > 30 years			
All participants	2.08	[1.35; 3.22]	<i>P</i> = 0.001
Primi-gravida	1.40	—	NS
Multi-gravida	2.04	[1.26; 3.30]	<i>P</i> = 0.003
Pre-gestational obesity (BMI > 27 kg/m <sup>2</sup> )			
All participants	1.96	[1.20; 3.20]	<i>P</i> = 0.007
Primi-gravida	2.40	—	NS
Multi-gravida	1.74	[0.99; 3.06]	<i>P</i> = 0.05
Paraguayan origin			
All participants	1.57	—	NS
Primi-gravida	1.06	—	NS
Multi-gravida	1.82	—	NS
First-degree relatives with diabetes mellitus			
All participants	1.17	—	NS
Primi-gravida	0.77	—	NS
Multi-gravida	1.53	—	NS
Previous GDM			
Multi-gravida	7.59	[3.98; 14.50]	<i>P</i> < 0.0001
Third trimester hypertension			
Multi-gravida	2.00	[1.18; 3.38]	<i>P</i> = 0.009
Previous macrosomia (newborn > 4 kg)			
Multi-gravida	1.75	[0.98; 3.14]	<i>P</i> = 0.05

NS non-significant

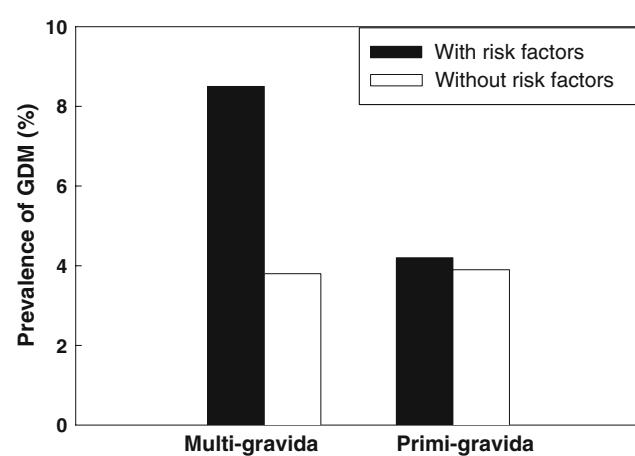
factor was significantly associated with an increase in GDM prevalence (i.e. a risk factor), we also calculated the 95% confidence interval for its OR (Table 3). In the population under study as a whole (all participants), we found the following risk factors for GDM: pre-gestational obesity, previous hyperglycaemia and age > 30 years. When we analysed MG subjects as a separate group we found the same risk factors as above, plus previous GDM and its surrogate markers previous macrosomia and third trimester hypertension. In nulliparous subjects (PG), none of the factors we analysed was found to be significantly associated with an increase in GDM prevalence (i.e. no risk factors for this group). In addition, we were unable to find a significant increase in risk for GDM in pregnant women who had first-degree relatives with diabetes mellitus (Table 3). Interestingly, we found that GDM prevalence tended to be greater among pregnant women of Paraguayan origin who live in La Plata (not observed with any other ethnic group). However, this did not reach statistical

significance, probably due to the fact that this group (mainly of mixed native Guarany and Spanish ethnic origin) constituted only 10% of all participants. The age and BMI of subjects of Paraguayan origin did not differ from that of our entire group.

#### Evaluation of the usefulness of selective screening for GDM

Firstly, we established the prevalence of risk factors for GDM in our subject group. We observed that 49.5% of all participants had at least one risk factor for GDM (this proportion increased to 58% in MG subjects, and decreased to 33.8% in PG subjects).

When evaluating our population under study as a whole, we found that of all the cases of GDM detected, only 65% presented one or more risk factors for GDM (and thus could have been detected by selective screening). We also found that in all participants, the prevalence of GDM in subjects without risk factors was 4.1%, significantly lower than GDM prevalence in subjects with risk factors (7.6%, *P* = 0.008 for difference between prevalence). This unexpectedly elevated prevalence of GDM in the absence of risk factors led us to evaluate selective screening for GDM in the sub-groups of PG and MG participants. We found a similar prevalence of GDM (approximately 4%) in PG subjects with and without risk factors (Fig. 1, non-significant difference between GDM prevalence in PG with or without risk factors for GDM). On the other hand, the prevalence of GDM in MG subjects with risk factors was more than twofold higher than in MG subjects without any risk factors (Fig. 1, *P* = 0.003 for difference between prevalence). However, GDM prevalence in MG women in



**Fig. 1** Relationship between prevalence and risk factors for GDM. In 24–28-week primi-gravida and multi-gravida unselected pregnant women of La Plata who were screened for GDM, prevalence of GDM was established both in the presence (solid bars) and absence (empty bars) of risk factors for GDM

**Table 4** Logistic regression model for GDM in 24–28-week pregnant women of La Plata

Risk factor (group under study)	$\beta$	P value	Exp( $\beta$ )
Age > 30 years			
All participants	0.577	0.012	1.781
Multi-gravida	0.604	0.017	1.830
Previous hyperglycaemia			
All participants	1.636	0.000	5.135
Multi-gravida	0.896	0.079	2.440
Previous GDM			
Multi-gravida	1.221	0.024	3.392
Constant			
All participants	-3.089	0.000	0.046
Multi-gravida	-3.086	0.000	0.046

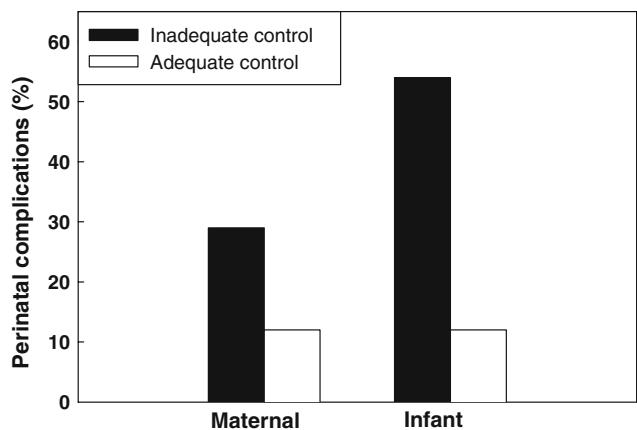
the absence of risk factors was similar to that of PG women (Fig. 1).

Logistic regression models were adjusted to determine a possible association between risk factors and GDM probability. For all participating subjects we found that a model that included previous hyperglycaemia and age > 30 years was predictive of GDM (Table 4). This model estimates that the probability to develop GDM in a pregnant woman over 30 years and with previous hyperglycaemia is 0.294 (fivefold higher than for all participants).

For MG subjects we found that a model that included previous hyperglycaemia, age > 30 years and previous GDM was predictive of GDM (Table 4). This model estimates that the probability to develop GDM in a MG pregnant woman, over 30 years, with previous hyperglycaemia and previous GDM, is 0.410 (sixfold higher than for all MG subjects). Finally, for PG subjects we were unable to find a logistic model with a good adjustment.

#### Post-diagnosis control of GDM and perinatal complications

Through post-natal analysis of maternal and infant clinical histories of subjects with GDM, we observed that in 48% of all subjects with GDM, post-diagnosis control was inadequate. This deficiency in GDM control tended to be severe: in 46% of these cases, laboratory diagnosis of GDM was not recorded in the clinical histories and/or there was no record of any obstetric control from the time of GDM diagnosis until delivery. When we addressed the frequency of perinatal complications attributable to GDM, we found that in the cases with inadequate control, infant complications were increased fourfold ( $P = 0.006$ ) compared to cases with adequate control (Fig. 2). Maternal complications also showed a tendency to increase, although this was not statistically significant ( $P = 0.12$ ).



**Fig. 2** Post-diagnosis obstetric control of GDM and perinatal complications. Post-natal analysis of maternal and infant clinical histories of subjects with GDM was performed, to determine maternal and/or infant perinatal complications attributable to GDM, as well as compliance with local guidelines for GDM management. Maternal and infant complications are shown as a percentage of pregnancies complicated by GDM with adequate (empty bars) or inadequate (solid bars) obstetric control post-diagnosis of GDM

#### Discussion

In this study, we screened for GDM and evaluated several parameters (ethnicity, anthropometric and metabolic status, family history of diabetes, prior obstetric complications and age, among others) in a large group of unselected, consecutively recruited 24–28-gestation week pregnant women who received their antenatal care in La Plata Primary Health Care centres.

Through the analysis of all the parameters studied and of the laboratory results for GDM screening, we were able to establish GDM prevalence and risk factors for our subject group, and found them to be in accordance with those reported by other authors for Argentine pregnant women [3, 12]. We then set out to evaluate the usefulness of implementing selective screening for the detection of GDM, which in our case is not a minor issue considering that approximately 50% of all participating subjects in this study did not have any risk factors for GDM. Unfortunately, we found an unacceptably high prevalence of GDM (approximately 4%) in participants without risk factors. Since around two-thirds of all participants in this study were multiparous (MG), and in this group risk factors for GDM were absent in over 40% of subjects (i.e. the greatest burden for diagnostic OGTTs to be performed in women without risk factors if screening must be universal), we decided to evaluate whether selective screening could be applicable in MG pregnant women. Our results for MG subjects show that, although the presence of risk factors more than doubles GDM prevalence, in the absence of risk factors, it is still

unacceptably high. In PG women the situation is even worse: GDM prevalence has the same baseline value (approximately 4%) in the presence or absence of risk factors for GDM.

These results preclude the application of selective screening for GDM in our population, indicating that all non-hyperglycaemic 24–28-week pregnant women must be tested for GDM (i.e. universal screening). In addition, since MG women with risk factors have a high prevalence of GDM (around 9%), in order to increase the sensitivity of GDM screening it could be recommendable to retest them with a 32-week OGTT if they were negative for GDM at 24–28 weeks. This, however, is not the case with PG pregnant women: in this group GDM prevalence is lower and independent of the presence or absence of risk factors, so they do not need to be retested when negative for GDM at 24–28 weeks.

Our present results are in agreement with recent reports, which have found universal screening for GDM to be more sensitive and cost-effective than selective screening in Italian [10], Spanish [11], Iranian [19], French [20, 21], Arab [22] and Polish [23] populations. The reports of Di Cianni et al. [10] and Corcoy et al. [11] are especially relevant in our case, since most of Argentina's population is of immigrant origin, predominantly of Italian and/or Spanish extraction (our present subject group is no exception). From the results presented by Di Cianni et al. [10] it can be estimated that for their Italian population, selective screening for GDM detected only 35% of the cases, which would have been diagnosed by universal screening, thus invalidating selective screening due to its unacceptably low sensitivity. In our present study, although we found a higher sensitivity for selective screening (65% of that of universal screening), it is still too low to recommend its implementation.

Screening for GDM is usually necessary for its timely detection, and this is a first step towards the reduction of its perinatal complications. However, detection alone is insufficient to achieve this goal. Laboratory diagnosis must be followed up by adequate treatment, which should be undertaken according to recommended guidelines. This has been demonstrated recently by the ACHOIS study, in which a significant reduction was observed for infant perinatal complications in pregnancies with GDM that received intensified care versus routine care [5]. In the present study, we present data which show that in La Plata (capital of the province of Buenos Aires) half of all women with laboratory diagnosis of GDM received inadequate post-diagnosis obstetric control, and consequently showed a significant increase in perinatal complications attributable to GDM. Our results underscore the importance of following guidelines or recommendations for the treatment of

GDM, since women with GDM who are treated adequately have a better prognosis. However, it is also important to audit the health care system in order to determine if there are sectors in which accessibility to health care services is sub-optimal. In this context, two recent reports have shown that universal screening for GDM improves its outcome (i.e. decreases perinatal complications), versus selective screening [21, 22]. Changing the method of GDM screening, for another of greater sensitivity, can be expected to influence the global frequency of related perinatal complications (due to the present detection of GDM in cases that would have escaped diagnosis with the prior less sensitive screening method). However, *a priori* this change of method would not be expected to affect the number of perinatal complications per case of diagnosed GDM, as reported by Cosson et al. [21] and Ezimokhai et al. [22]. A possible explanation for this could be a greater awareness of GDM and of its recommended treatment as a consequence of the education of health care professionals and the general public, which would be necessary to implement a change in the screening method for GDM. This explanation is supported by our present results showing that women with GDM, who are treated according to recommended guidelines, have a better perinatal prognosis.

In conclusion, due to the poor sensitivity that we have found for selective screening of GDM, universal screening must be recommended in our population. Thus, all non-hyperglycaemic 24–28-week pregnant women should be tested for GDM with an OGTT, and particular attention must be paid to MG women with risk factors for GDM: if negative at 24–28 weeks, they may be retested at 32 weeks. In order to reduce the perinatal complications of GDM, laboratory diagnosis must be followed up by adequate treatment, which should be undertaken according to recommended guidelines.

## Collaborators

The following Obstetricians and Biochemists collaborated in this study: M. C. Benavidez, P. Bernard, S. Blanco, D. Boán, M. Boccia, G. Bolzicco, P. Burgat, L. Cáceres, V. Calabrese, R. Candau, A. Ciscato, C. Corti, A. M. Cortizo, G. de Medero, A. de Orta, C. del Soldato, G. di Loretto, G. Díaz Bartolomé, G. Garbalena, M. Giovannone, S. González Yunk, M. C. González, S. Gustavson, M. C. Jurado Sidereff, C. Kerai, N. Laguna, P. Manzanares, E. Martínez, C. Masson, G. Matkowski, M. Mendoza, C. Morcella, M. Mulatero, C. Olmos, M. J. Peláez, N. Petrucci, F. Portas, I. Rivas Pinedo, S. Salguero, A. Stefanizzi, F. Suárez Crivaro, R. Toro, A. Uriarte, D. Vilte, N. Vitar, Y. Wilt, A. Zeballos, A. Zuaznabar, M. Zubietra.

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