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Contents

EDITORIAL

Emergence of novel coronavirus SARS-CoV2 in China and the response in Mexico

Emergencia del coronavirus SARS-CoV2 en China y la respuesta en México

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Mais il vient toujours une heure dans l'histoire où celui qui ose dire que deux et deux font quatre est puni de mort.

— La Peste, Albert Camus

The pneumonia epidemic caused by an unknown pathogen started on December 8, 2019;[1] on December 31, Chinese health authorities reported to the World Health Organization (WHO) a series of cases in the city of Wuhan, Hubei Province, China.[2] The WHO responded quickly by coordinating the development of the diagnosis, providing guidance on patient monitoring, sample collection and treatment, and by updating the information on the outbreak.[3] Most cases were epidemiologically associated with a market in Wuhan where live animals are sold (Huanan Seafood Wholesale Market), which suggests a possible zoonotic origin (transmission from animals to humans).[4] On January 7, 2020, isolation and identification of the pathogen was achieved using next-generation sequencing in samples of bronchoalveolar lavage fluid from a critically ill patient.[5,6]

On January 12, 2020, the Chinese authorities shared the complete genome sequence of a new viral strain of the *Coronaviridae* family, which was initially called 2019-nCoV.[7] Previously, six coronavirus species that cause human infections were known; two of them, the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), are zoonotic microorganisms that cause severe acute respiratory infections, usually fatal.[8] 2019-nCoV was found to belong to the betacoronavirus 2B lineage, to have formed a clade within the *sarbecovirus* subgenus, *Orthocoronavirinae* subfamily, and to share 82 % of genomic sequence with SARS-CoV.[9,10] Because of this, this coronavirus was designated as SARS-CoV2. The explosive nature of the outbreak and rapid spread of the disease drew the attention of the international community.

In this context, there are two elements that are important to understand SARS-CoV2 rapid spread:

- The epidemic started in a country with more than 1400 million inhabitants (Wuhan alone has 11 million residents).
- It coincided with a substantial increase in the number of trips within China and abroad, around the Lunar New Year on January 25, 2020. (According to the National Development and Reform Commission of China, between January 10 and February 18, 2020, more than 3 billion passenger trips would have been carried out by all means of transport).[11]

Information on the SARS-CoV2 outbreak has been generated and shared "in real time" thanks to new molecular diagnostic technologies and new information platforms. By January 31, 2020, 46 complete genomes were already available in public and private databases such as GenBank (https//www.ncbi.nlm.nih.gov/genbank/2019-ncov-seqs/) and GISAID (https//www.gisaid.org), with fully-developed phylogenomic trees and phylodynamic analyses. All this happens, fortunately, when most specialized scientific

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journals have already migrated to electronic formats on the Internet (many of them open access). Some medical journals are offering to share information with other publishing houses and with the WHO, even prior to publishing their final versions.[12] Websites specializing in infectious diseases and expert social networks, such as ProMED-mail (https//promedmail.org/) and Virological (http//virological.org/), have discussion forums on the subject; some academic (https//www.worldometers.info/coronavirus/coronavirus-cases/) and university (https//gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6) efforts are spreading real-time information. All over the world, the coordinated efforts of academics from very diverse disciplines have been essential to ensure the timeliness and quality of information.

As of February 5, 2020, at least 24,554 cases and 492 deaths have been confirmed in 24 countries from five of the six WHO regions. The proportion of serious cases is 13.2 %, with a case fatality rate of 2.1 %.[13] Incubation period has been estimated to be 5.2 days (95 % CI = 4.1-7.0,).[14] During the first weeks, the epidemic was doubling every 7.5 days,[15] and the basic reproductive number was estimated at between 2.2 and 3.5.[16,17] Since early December 2019, there is evidence of person-to-person transmission among close contacts;[18] however, we still need more epidemiological information to integrate predictive models of the pathogenic potential, virulence and transmissibility dynamics of this new virus.

Considering the risk international spread of the SARS-CoV2 outbreak represents, and that a coordinated global response is required, the WHO Emergency Committee declared a Public Health Emergency of International Concern (PHEIC) on January 30, 2020.[19] This decision means that the situation is serious, sudden, unusual and unexpected. PHEICs generate situations that negatively affect, in one way or another, large groups of the population, but they also represent an important opportunity to learn from diseases and pathogens, as well as from our strengths and weaknesses, to control them and respond to their occurrence.[20]

As for Mexico, the Ministry of Health initially disseminated materials with general information on the status of the SARS-CoV2 epidemic. On January 30, 2020, the Epidemiological and Health Intelligence Unit, a focal point in our country for WHO's International Health Regulations,[21] issued a preventive warning on travelling to the Hubei Province in China; every day, a report with verified data from official sources is updated.[22]

In operational terms, the National Committee for Health Security held an extraordinary session in order to activate the Technical Subcommittee on Emerging Diseases, which is the body responsible for establishing and coordinating the actions for preparedness and response in the health sector.[23] The National Epidemiological Surveillance System (SiNaVe – *Sistema Nacional de Vigilancia Epidemiológica*) published the "Standardized guidelines for epidemiological and laboratory surveillance of 2019-nCoV-related disease", a document that establishes operational definitions, prevention and control measures, handling of samples, a diagnostic algorithm and biological risk management in the face of the imminent emergence of this disease in Mexico.[24] As of February 5, SiNaVE has detected 10 suspicious cases, all ruled out by the Institute of Epidemiological Diagnosis and Reference, the first national reference laboratory to develop the methodology for the confirmation of cases in Latin America.[25] An article appearing in *Gaceta Médica de México* number 2 of 2020 reviews the development of the epidemic in the world and the prevention and control actions suggested in the country.[26]

Since the appearance of SARS-CoV in 2003 and MERS-CoV in 2012, we have learned of a new coronavirus every decade. Communicable diseases caused by new coronaviruses most likely will continue to emerge in the future. Currently, there is no specific treatment or vaccine that prevents SARS-CoV2 transmission, and health workers represent a population at risk; therefore, it is important for biosafety measures to be strengthened in public health laboratories and all medical units as soon as possible.

All stakeholders involved in the response to this emergency –from clinicians (general practitioners and primary, secondary and tertiary care specialists), scientists (experts in virology, molecular biology and bioinformatics), the editorial community (authors, reviewers, editors) and public health specialists to the organized civil society– we all must collaborate with real-time knowledge and information in order for health authorities' decisions to have a real impact on public health.

The response of us all to the emergence of SARS-CoV2 must imply a deep sense of commitment and social action to the benefit of public health.

Conflict of interests

None.

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ORIGINAL ARTICLE

Demand for obstetric care and density of health resources for childbearing age Mexican women

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Abstract

Introduction: *In Mexico, there is an increase recorded in the number of C-sections, as well as inequity and inequality in the distribution of resources for obstetric care.* **Objective:** *To identify the states and municipalities in Mexico that concentrate the demand for obstetric care and the C-section rates and their relationship with health resources and women of childbearing age (WCBA).* **Method:** *Births of the 2008-2017 period were recorded, grouped into five municipal strata, as well as 2017 health resources and WCBA.* **Results:** *The 2008-2017 national rate of C-sections was 45.3/100 births; 95 and 97 % of births and C-sections were concentrated in the "very high" stratum, where 80 % or more of health resources were used, with overuse standing out. The density of health resources assigned to WCBAs reflected inequity and inequality.* **Conclusions:** *The high concentration of obstetric demand and health resources supply could entail a higher recurrence of C-sections. Policies for C-section reduction should consider proper organization and administration of health resources.*

KEY WORDS: *Maternal health services. Cesarean sections. Health resources. Woman of childbearing age.*

Demanda de atención obstétrica, cesáreas y densidad de recursos en salud para la población femenina en edad fértil de México

Resumen

Introducción: *México registra aumento de las cesáreas e inequidad y desigualdad en la distribución de recursos para la atención obstétrica.* **Objetivo:** *Identificar las entidades y municipios en México que concentran la demanda de atención obstétrica y tasas de cesáreas y su relación con los recursos en salud y mujeres en edad fértil (MEF).* **Método:** *Se registraron los nacimientos del periodo 2008-2017, agrupados en cinco estratos municipales, y los recursos en salud y MEF de 2017.* **Resultados:** *La tasa nacional de cesáreas 2008-2017 fue de 45.3/100 nacimientos; 95 y 97 % de los nacimientos y cesáreas se concentraron en el estrato "muy alto", en el cual se utilizó 80 % o más de los recursos en salud y destacó la sobreutilización. La densidad de recursos en salud destinados a las MEF reflejó inequidad y desigualdad.* **Conclusiones:** *La alta concentración de la demanda obstétrica y oferta de los recursos en salud pudiera conllevar mayor recurrencia a la cesárea. En las políticas de reducción de cesáreas es necesario considerar la organización y administración adecuadas de los recursos en salud.*

PALABRAS CLAVE: *Servicios de salud materna. Cesáreas. Recursos en salud. Mujeres en edad fértil.*

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Introduction

There are two routes whereby a delivery is solved: vaginal delivery or cesarean section (C-section). Regardless of the route, there is a natural risk for the mother and the fetus, and the obstetrician must therefore judge case by case which option is best for both.[1,2]

C-section is an incision in the abdominal and uterine walls that is intended to extract the living or dead fetus of 22 or more weeks of gestation, as well as the placenta and its annexes. It is the most common surgical procedure in obstetrics departments and its indication is the responsibility of the specialist in that area in daily practice.[3,4]

The indications for C-section are precise and its only purpose is to ensure the mother-child binomial health, and thus this surgical procedure should only be used in women with high-risk deliveries.[2,5,6] When it is carried out without the precise indications being complied with, the risks outweigh the benefits, which generates complications for women, violations of their reproductive rights and additional costs for the health system.[7,8]

The cesarean section rate (CSR) is a multidimensional indicator of hospital performance that assesses adequate medical care, mother-child safety and efficiency in the use of resources. According to the World Health Organization, the rate of necessary C-sections is estimated to range between 10 and 15 % of deliveries, while the CSR to reduce maternal-neonatal health risks ranges from 15 to 20 %.

Since 2000, an increase in CSR and its related factors has been reported in Mexico.[9-12] With regard to clinical factors, in a review of 3232 medical records from the Mexican Institute of Social Security for the 1997-1999 period, 434 diagnostic expressions were noted, a heterogeneity that contrasted with institutional regulations in force, which established 59 specific indications.[13]

Differential CSRs have been referred when comparing different states of the country according to their degree of marginalization; the highest rates show a positive association with socioeconomic development: the lower the marginalization, the higher the CSR and vice versa.[14]

Studies on the organization of health services have found that CSRs are higher in the private than in the public sector, and that, in the latter, the CSR is higher in social security institutions than in those that look after unaffiliated population.[10,14]

In Mexico, iniquity and inequality in the distribution of health resources in general and specifically for obstetric care have been pointed out.[14-16]

Regarding the size of hospitals, Campero et al. identified that the probability of C-section in a woman who requires obstetric care increases according to the size of the hospital from 10 beds on.[17]

Since 1983, several constitutional reforms have been carried out in Mexico in order to achieve the right to health protection and universal health coverage; however, inequality gaps persist. One of the causes is the supply of health resources, which is governed by social demand for medical care rather than by demographic and health requirements,[18] which results in divergences in their use or efficiency, estimated as the volume of actions per unit of available health resources and the density of health resources (DHR), which refers to the ratio between the resources available to meet health needs and the target population they are directed to, even when they are not necessarily available at a given moment for that population.[15]

Objectives

- To identify the states and municipalities where the highest demand for obstetric care is concentrated, considered on the basis of the births recorded in the 2008-2017 period and the highest C-section rates, through stratification and mapping of information.
- To analyze the statistical relationship between the municipal strata according to the demand for obstetric care and C-sections and the efficiency of health resources in the municipalities.
- To identify the municipalities where the highest number of women of childbearing age (WCBA) aged 15 to 44 years is concentrated through municipal stratification and its statistical and geospatial relationship with the demand for obstetric care and C-sections and DHR per municipality.

Method

CSRs were calculated by states and municipalities according to the natality databases of the National Institute of Statistics and Geography (INEGI – *Instituto Nacional de Estadística y Geografía*) and the Ministry of Health (SSa – *Secretaría de Salud*) for the 2008-2017 period. Births of 22 or more weeks of gestation and ≥ 500 g weight were taken into account.

For the calculation of the CSR, the state and municipality of birth, the place where pregnant women

requested and received the delivery care were taken into account.

The analysis by state of birth and annual CSR showed no significant differences, and the information for the period was therefore accumulated; the same procedure was used in the analysis by municipalities with the purpose to stabilize the CSRs.

For the summary and analysis of data by states and municipalities, births and CSRs were grouped by strata: very low (VL), low (L), middle (M), high (H) and very high (VH). The stratification method was by percentiles. Stratification according to the number of births was used as the basis of the analysis for the grouping of the remaining data.

A concordance study between strata by birth and C-section was performed separately for both the states and municipalities in order to identify the relationship between both variables.

For better representation of some data, mapping was used. For the generation of maps, the Digital Map of Mexico program, version 6.3.0, was used, as well as the map layers of all 32 states of the country and their 2458 municipalities developed by INEGI.

The 2017 Health Resources data were acquired from the SSa General Directorate of Health Information and those for WCBA, from the 2017 projections of the National Population Council.

In order to analyze the statistical significance of differences, CSR mean comparisons were performed by strata using error plots and single-factor analysis of variance (ANOVA). The chi-square test was also used for the comparison of CSRs by strata.

Results

The number of births with state of birth records was 20,179,539 (Fig. 1). The VH and H strata concentrated 67.9 % of births, as well as 69.5 % of 9,141,552 C- sections performed during the period.

A national CSR of 45.3/100 births was estimated. By states, the CSR ranged from 31.2 to 52.2/100 births. The five states with the highest CSRs were Nuevo León, Yucatán, Sinaloa, Mexico City and Tamaulipas, while those with the lowest CSRs were San Luis Potosí, Zacatecas, Nayarit, Chiapas and Durango.

By strata, no differences in rates were identified, which ranged from 42.5 to 47.6/100 births, not statistically significant according to the mean contrast plot and the ANOVA. The error plot shows CSR wide intervals for each stratum, which overlap with the opposites. The chi-square test for CRSs showed no significant differences between strata.

Geospatial contrast of births and CSR data shows that stratifications barely reached a concordance of 6.3 % (Fig. 1).

Births with a municipal registry were 20,176,197 (Fig. 2). There were 109 municipalities (4.43 %) with no data.

According to stratification, births and C-sections were concentrated in the VH stratum, which comprised 470 municipalities, with 95 and 97 %, respectively. Furthermore, CSR in that stratum was the highest: 46.3/100 births. CSR mean differences by strata are statistically significant, particularly when the VH stratum is compared with the others, according to the error plot and the ANOVA results. The narrow confidence intervals in the error plot for each stratum indicate stable figures inside. VH versus H stratum rate ratio is 1.58 and 5.1 in comparison with the VL stratum.

Concordance between municipalities of birth and CSR was 55.3 %; however, the analysis for each stratum showed a concordance of 93 % between the VH strata of both groups. There was an almost perfect spatial correlation between the municipalities localized in the VH stratum of births and those of the CSR VH stratum, which increased the reliability of the trend towards concentrating the demand for obstetric care and C-sections in these municipalities.

Table 1 describes the use of health resources by municipal strata according to the demand for obstetric care. In the majority of them, an upward trend was found that ran parallel to birth stratification: from lower to higher number of births, lower to higher use of health resources. With the exception of 11 items, the VH stratum concentrated 80 % or more of resources. In those that had percentages lower than this limit, concentration was equal to or greater than 70 % when the immediately lower stratum was added, with a predominance of the VH stratum, which confirms the trend towards a concentration of resources.

Table 2 shows the efficiency of health resources. Except for three items within births and two in C-sections, an ascending number of births or C-sections was found per unit that ran parallel to birth stratification: from lower to higher birth stratification, lower to higher number of births or C-sections per unit of health resources, which indicates overuse in the VH and underuse in the VL strata.

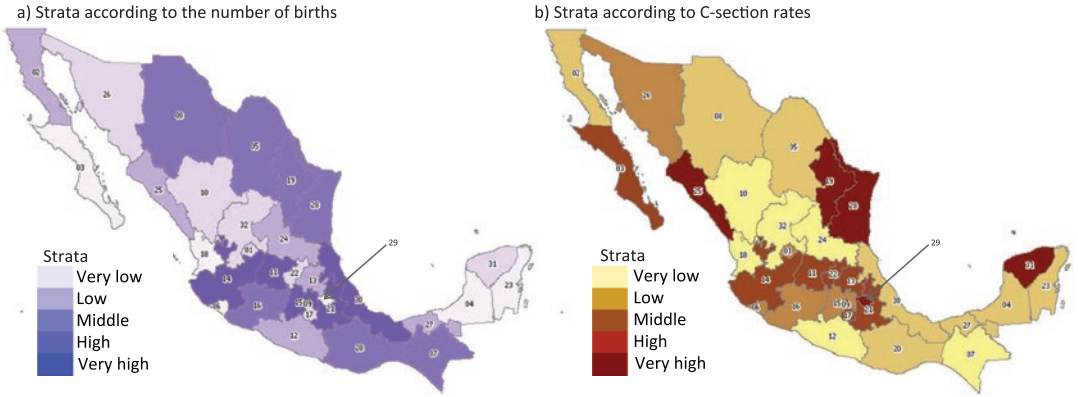
As for the distribution of WCBA by strata according to the number of births (Fig. 3), nearly 75 % of WCBA were at the VH stratum, followed by the H

Rates of C-sections by state, stratified according to obstetric demand during the decade

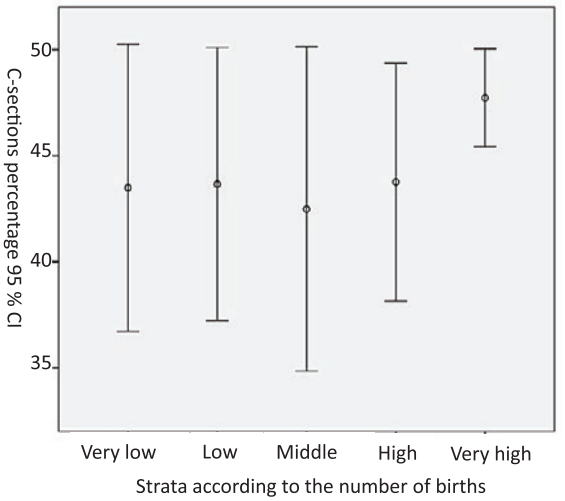
State Strata	Births	C-sections	C-section rate*	% total national Births	 C-sec.
18 Nayarit	183 687	58 816	32.0	---	---
23 Quintana Roo	253 822	105 525	41.6	---	---
04 Campeche	145 115	61 644	42.5	---	---
06 Colima	130 115	61 061	46.9	---	---
03 B California Sur	116 856	56 502	48.4	---	---
29 Tlaxcala	236 758	117 231	49.5	---	---
Very low	**1 066 353**	**460 779**	**43.2**	**5.3**	**5.0**
32 Zacatecas	286 984	90 396	31.5	---	---
10 Durango	318 372	116 519	36.6	---	---
01 Aguascalientes	270 589	123 128	45.5	---	---
26 Sonora	449 735	204 464	45.5	---	---
22 Querétaro	391 102	185 214	47.4	---	---
17 Morelos	314 990	151 988	48.3	---	---
31 Yucatán	345 120	175 317	50.8	---	---
Low	**2 376 892**	**1 047 026**	**44.1**	**11.8**	**11.5**
24 S Luis Potosí	470 679	146 916	31.2	---	---
12 Guerrero	552 980	204 026	36.9	---	---
02 B California	524 274	228 157	43.5	---	---
27 Tabasco	497 222	219 119	44.1	---	---
13 Hidalgo	476 863	231 964	48.6	---	---
25 Sinaloa	503 436	254 502	50.6	---	---
Middle	**3 025 454**	**1 284 684**	**42.5**	**15.0**	**14.1**
07 Chiapas	777 866	268 235	34.5	---	---
08 Chihuahua	588 241	226 065	38.4	---	---
05 Coahuila	554 363	237 643	42.9	---	---
20 Oaxaca	625 776	276 508	44.2	---	---
16 Michoacán	833 807	371 278	44.5	---	---
28 Tamaulipas	609 763	302 406	49.6	---	---
19 Nuevo León	834 032	435 282	52.2	---	---
High	**4 823 848**	**2 117 417**	**43.9**	**23.9**	**23.2**
30 Veracruz	1 170 016	516 786	44.2	---	---
15 México	2 608 367	1 211 201	46.4	---	---
11 Guanajuato	1 135 557	538 971	47.5	---	---
14 Jalisco	1 396 229	684 172	49.0	---	---
21 Puebla	1 153 267	564 954	49.0	---	---
09 Mexico City	1 423 556	715 562	50.3	---	---
Very high	**8 886 992**	**4 231 646**	**47.6**	**44.0**	**46.3**
Total	**20 179 539**	**9 141 552**	**45.3**	100.0	100.0

* Per hundred births

Distribution of states according to the number of births or obstetric demand (a) and C-section rates (b)



Mean contrasts: C-section rates by strata according to the number of births

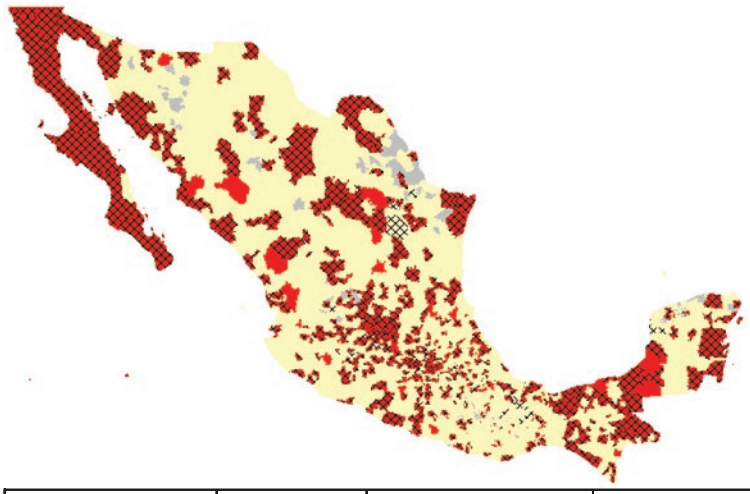


Single-factor ANOVA

C-section rates per strata (States)

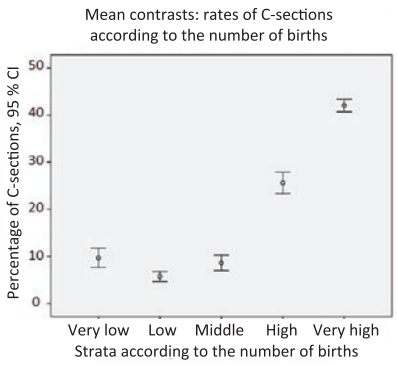
	Sum of squares	df	Quadratic mean	F	Sig.
Inter-group					
Combined	99.103	4	24.776	0.662	0.624
Linear term					
Non-weighted	45.681	1	45.681	1.221	0.279
Weighted	43.111	1	43.111	1.152	0.293
Deviation	55.992	3	18.664	0.499	0.686
Intra-group	1010.244	27	37.416		
Total	1109.347	31			

Figure 1. *Obstetric demand (number of births) and C-section rates, nation-wise and by states. Mexico, 2008-2017.*



Strata by number of births		Municipalities* n	Births n	Births %	C-sections n	C-sections %	C-section rates**
	Very low	470	1 991	0.01	180	0.00	9.04
	Low	469	13 965	0.07	678	0.01	4.85
	Middle	469	91 544	0.45	8 864	0.10	9.68
	High	471	910 593	4.51	265 964	2.91	29.21
	Very high	470	19 158 104	94.95	8 864 862	96.98	46.27
	Total	2 349	20 176 197	100.00	9 140 548	100.00	45.30

Municipalities at the "very high" stratum of C-section rates.
*109 municipalities with no data. Total municipalities in 2017: 2458
** Per hundred births



Single-factor ANOVA
C-section rates per strata (Municipalities)

	Sum of squares	df	Quadratic mean	F	Sig.
Inter-group					
Combined	442370.9	4	110592.7	303.3	.000
Linear term					
Non-weighted	335783.4	1	335783.4	920.9	.000
Weighted	335693.4	1	335693.4	920.7	.000
Deviation	106677.6	3	35559.2	97.5	.000
Intra-group	854642.8	2344	364.6		
Total	1297013.7	2348			

Figure 2. *Obstetric demand and C-section rates distribution according to municipal strata and their geospatial coincidence. Mexico, 2008-2017. Source: Bases de datos abiertas de nacimientos, INEGI/SSA, 2008-2017.*

stratum, which together accounted for approximately 88 %. This distribution is geospatially illustrated on the map: it exceeds the territorial extension of the 470 municipalities where 95 % of births are concentrated.

Women in the VH stratum who migrated for their care were 41.1 %, while 34.5 % in the H stratum and 29.6 % in the VL stratum did the same. The DHR figures for WCBA have a random behavior, since some of them reflect iniquity and inequality in the provision of resources, while there are also similar figures that would indicate equity and equality.

Discussion

Currently, ecological studies at the level of small areas are more convenient because they are more enlightening.[19] With this approach, in our analysis we identified a high concentration in the demand for obstetric care and C-sections in 470 municipalities associated with the clustering of health resources. However, inequalities were observed in the use of health resources in the H and VH strata, with overuse due to the excessive demand for obstetric care. Regarding human resources for health, this relationship can be considered as an indicator of

Table 1. Health resources distribution by municipal strata according to the number of births or obstetric demand. Mexico, 2008-2017

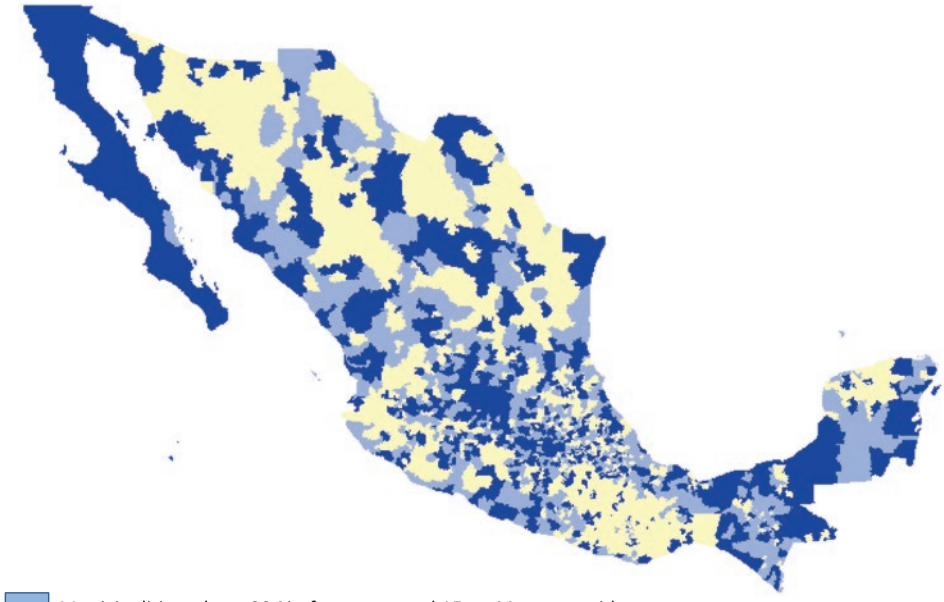
Health resources	Strata according to the number of births										
	Very low		Low		Middle		High		Very high		Total
	n	%	n	%	n	%	n	%	n	%	
Primary care units	1228	5.9	1887	9.1	2969	14.4	4702	22.7	9883	**47.8**	20669
Secondary care units	2	0.2	6	0.5	20	1.5	232	17.7	1050	80.2	1310
Hospitalization area	2	0.1	9	0.5	29	1.7	260	14.8	1455	82.9	1755
Surgical unit	0	0.0	1	0.1	12	1.0	208	17.7	951	81.1	1172
NICU	0	0.0	0	0.0	1	0.3	8	2.3	333	97.4	342
Obstetrics and obstetric surgery area	56	3.6	67	4.3	86	5.5	327	21.0	1021	**65.6**	1557
Neonatology and nursery area	1	0.1	5	0.6	13	1.6	105	12.7	701	85.0	825
Operating rooms	2	0.0	3	0.1	19	0.5	314	7.7	3714	91.7	4052
Delivery rooms	100	3.8	169	6.4	214	8.1	528	20.0	1632	**61.7**	2643
Cribs for healthy newborns	31	0.4	49	0.7	71	1.0	480	6.6	6599	91.3	7230
Total offices	1864	2.5	2832	3.8	4410	5.9	9016	12.2	56036	**75.6**	74158
General medicine	1508	3.9	2274	5.9	3457	8.9	6184	15.9	25355	**65.4**	38778
Obstetrics & gynecology	2	0.1	6	0.3	27	1.3	229	11.4	1746	86.9	2010
Pediatrics	3	0.2	4	0.2	26	1.5	186	10.7	1527	87.5	1746
Total beds hospitalization area	15	0.0	250	0.3	570	0.7	4074	4.7	82014	94.4	86923
General medicine	3	0.2	6	0.4	42	2.9	540	36.9	874	**59.7**	1465
Obstetrics & gynecology	1	0.0	15	0.1	48	0.3	983	5.9	15533	93.7	16580
General and reconstructive surgery	0	0.0	6	0.0	32	0.2	643	4.6	13347	95.1	14028
Pediatrics	4	0.0	14	0.1	105	1.0	683	6.2	10131	92.6	10937
Labor area	199	4.0	327	6.5	442	8.8	631	12.5	3438	**68.3**	5037
Postpartum recovery area	0	0.0	8	7.8	14	13.6	4	3.9	77	**74.8**	103
Total physicians	1078	2.1	1984	3.8	3528	6.7	8178	15.6	37605	**71.8**	52373
General practitioners	189	1.0	210	1.1	261	1.4	824	4.3	17716	92.3	19200
Pediatricians	19	0.2	6	0.1	26	0.2	398	3.7	10356	95.8	10805
Obstetrician-gynecologists	14	0.2	3	0.0	31	0.3	408	4.5	8525	94.9	8981
Surgeons	14	0.2	3	0.0	7	0.1	128	1.8	6986	97.9	7138
Anesthesiologists	2	0.1	18	1.1	10	0.6	12	0.8	1531	97.3	1573
On training	759	5.9	978	7.6	1235	9.6	2047	15.9	7854	61.0	12873
Residents	96	0.6	127	0.8	264	1.7	794	5.1	14339	91.8	15620
Interns	96	2.7	185	5.2	269	7.5	353	9.9	2673	74.7	3576
Undergraduate interns	0	0.0	1	0.0	9	0.0	232	0.9	24287	99.0	24529
Total nurses	740	0.5	1228	0.8	2682	1.8	7664	5.2	133671	91.6	145985
General nurses	75	0.2	86	0.2	224	0.6	781	2.2	34647	96.7	35813
Obstetrics nurses	1012	0.5	1354	0.7	2936	1.4	11220	5.4	191723	92.1	208245

Source: *Bases de datos abiertas de nacimientos INEGI/SSa, 2008-2017* and SSa 2017 health resources. NICU = Neonatal intensive care unit.

Table 2. Use of heath resources by municipal strata according to obstetric demand or number of births. México, 2008-2017

Health resources	Strata according to the number of births					
	Very low	Low	Middle	High	Very high	Total
	HR/B or C ratio	HR/B or C ratio	HR/B or C ratio	HR/B or C ratio	HR/B or C ratio	HR/B or C ratio
Number of births	1 991	13 965	91 544	910 593	19 158 104	20 176 197
Obstetrics and obstetric surgery area	36	208	1064	2785	18764	12958
Delivery rooms	20	83	428	1725	11739	7634
General medicine offices	1	6	26	147	756	520
Obstetrics & gynecology offices	996	2328	3391	3976	10973	10038
Obstetrics & gynecology beds	1991	931	1907	926	1233	1217
Labor area beds	10	43	207	1443	5572	4006
Postpartum recovery beds	0	1746	6539	227648	248807	195885
General practitioners	11	67	351	1105	1081	1051
Obstetrician-gynecologists	142	4655	2953	2232	2247	2247
Anesthesiologist physicians	996	776	9154	75883	12513	12827
Medical interns	21	75	340	2580	7167	5642
Undergraduate interns	0	13965	10172	3925	789	823
Nurses	3	11	34	119	143	138
General nurses	27	162	409	1166	553	563
Obstetrics nurses	2	10	31	81	100	97
Number of C-sections	180	678	8 864	26 5964	8 864 862	9 140 548
Obstetrics and obstetric surgery area	3	10	103	813	8683	5871
Delivery rooms	2	4	41	504	5432	3458
General medicine offices	0	0	3	43	350	236
Obstetrics & gynecology offices	90	113	328	1161	5077	4548
Obstetrics & gynecology beds	180	45	185	271	571	551
Labor area beds	1	2	20	421	2578	1815
Postpartum recovery beds	0	85	633	66491	115128	88743
General practitioners	1	3	34	323	500	476
Obstetrician-gynecologists	13	226	286	652	1040	1018
Anesthesiologist physicians	90	38	886	22164	5790	5811
Medical interns	2	4	33	753	3316	2556
Undergraduate interns	0	678	985	1146	365	373
Nurses	0	1	3	35	66	63
General nurses	2	8	40	341	256	255
Obstetrics nurses	0	1	3	24	46	44

Source: *Bases de datos abiertas de nacimientos INEGI/SSA 2008-2017* and SSa 2017 health resources. HR = health resources. B = births, C = C-sections.



Municipalities where 88 % of women aged 15 to 44 years reside
Municipalities where 95 % of deliveries were attended to in the studied period

Indicator	Strata according to the number of births					
	Very low	Low	Middle	High	Very high	Total
Women aged 15 to 44 years	620,148	1,122,688	1,883,577	3,900,111	22,350,537	29,877,062
Percentage	2.1	3.8	6.3	13.1	74.8	100.0
Percentage of births with usual residence other than the municipality of care	29.6	20.6	18.3	34.5	41.1	40.7
2017 health resources	**Density of health resources use by women aged 15-44 years**					
Obstetrics and ob-surgery area	11,074	16,757	**21,902**	11,927	**21,891**	19,189
Delivery rooms	6,201	6,643	**8,802**	7,387	**13,695**	11,304
General medicine offices	411	494	545	**631**	**882**	770
Obstetrics & gynecology offices	**310,074**	**187,115**	69,762	17,031	12,801	14,864
Obstetrics & gynecology beds	**620,148**	**74,846**	39,241	3,968	1,439	1,802
Beds in labor area	3,116	3,433	4,261	**6,181**	**6,501**	5,932
Beds in postpartum recovery	0	140,336	134,541	**975,028**	**290,267**	290,069
General practitioners	3,281	**5,346**	**7,217**	4,733	1,262	1,556
Obstetrician-gynecologists	**44,296**	**374,229**	**60,761**	9,559	2,622	3,327
Physician anesthesiologists	**310,074**	62,372	**188,358**	**325,009**	14,599	18,994
Medical interns	6,460	6,069	7,002	**11,048**	**8,362**	8,355
Undergraduate interns	0	**1,122,688**	**209,286**	16,811	920	1,218
Nurses	**838**	**914**	702	509	167	205
General nurses	8,269	**13,055**	**8,409**	4,994	645	834
Obstetrics nurses	613	**829**	**642**	348	117	143

Figure 3. *Relationship between health resources and women aged 15 to 44 years by municipal strata according to obstetric demand or number of births. Mexico, 2008-2017. Source: Bases de datos abiertas de nacimientos, INEGI/SSA, 2008-2017. SSa 2017 health resources and National Population Council 2017 population estimates.*

productivity. As for the results, supersaturation in obstetrics and gynecology departments might lead to a higher use of C-section as a strategy to free beds in the delivery rooms, considering the effective time of care required for a vaginal delivery in comparison with a C-section.

Since its creation in the 1950s, the Mexican medical model has focused on curative or problem-solving care,[20] which places the delivery rooms in the hospital setting, privileging secondary and tertiary over primary care, thus transforming obstetric practice into a matter of "medical specialty" in parallel to the process of displacement of general medicine: there are 1.7 medical specialists for each general practitioner (Table 1).

During the study period, 98 % of births were attended to in hospitals; 63 % of the obstetrics and obstetric surgery areas, 93 % of neonatology and nursery areas, 95 % of operating rooms, 56 % of delivery rooms and 93 % of the cribs for healthy newborns are in secondary care facilities. In contrast, 92 % of general medicine offices, 83 % of general practitioners and 3 % of family medicine specialists are found in primary care units.

The results confirm the distributive health policy implemented in Mexico, which overlooks the criterion of the potential user population for the provision of services. This study highlighted the uneven DHR in relation to the number of WCBA, which might explain the high percentage of pregnant women inter-municipal migration for childbirth care to municipalities with more resources or that were available at the time they were required. Two out of every five childbirths were extraterritorial to the place of maternal usual residence. Although local density of resources in the L and VL birth strata was better, there was a high percentage of care in other municipalities, either because health resources were concentrated there or because local obstetric care services were not operating at the time they were required.

According to the results, inadequate planning of health resources for obstetric care and the medical care model are added to the known factors associated with high CSR and thus, considering these dimensions in the development of public policies aimed at reducing C-section rates is also required.

In this reengineering, designing primary care units with an acceptable area for the care of imminent or low-risk deliveries would be necessary, considering the distribution of the demanding population and the necessary health resources, in addition to strengthening primary care services, which also requires improving general practitioners capabilities and the quality of care.

Furthermore, estimating an adequate and rational CSR according to the context of the country is necessary, which will serve as a reference for further evaluations on C-sections, under the current regulations of delivery care. In addition, rational indicators of productivity and use of health resources are required.

Changes in the demographic and epidemiological profile of the Mexican population are foreseeable for the years to come. The health system needs to be adjusted to respond to these changes, especially including the composition of human resources, particularly towards vaginal route obstetric care.

The approach of this research report offers novel and important conclusions within the context the country is living in.

Acknowledgements

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REVIEW ARTICLE

Head & neck cancer. Its impact on the history of mankind

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Abstract

Squamous cell carcinoma is the most common head & neck malignancy, and its first descriptions date from the pharaonic era. It has impacted humanity by affecting labor, scientific and cultural productivity and, sometimes, it has influenced the course of history. Head & neck cancer is more common in economically impoverished countries and individuals; however, it can affect any socioeconomic stratum; it has been suffered by known, famous, economically powerful celebrities, intellectuals and artists. Head & neck cancer treatment has been controversial since its initial description up to the present day. Therapeutic decisions have been influenced not only by the stage but by the patient's environment and, sometimes, in an effort to reduce the morbidity resulting from the various oncological treatments, erroneous decisions have been made that have implied the loss of the patient's life. Unfortunately, currently we continue to see these behaviors. A synthesis of cases of renowned celebrities that suffered from this cancer is presented, and the impact this implied in the society of their times is described.

KEY WORDS: *Squamous cell carcinoma. Head. Neck. History of medicine.*

Cáncer de cabeza y cuello. Su impacto en la historia de la humanidad

Resumen

El cáncer epidermoide es el más frecuente en cabeza y cuello y sus primeras descripciones datan de la época faraónica. Ha impactado en la humanidad al afectar la productividad laboral, científica y cultural y, en ocasiones, ha influido en el derrotero de la historia. El cáncer de cabeza y cuello es más frecuente en países e individuos depauperados económicamente, sin embargo, puede afectar cualquier estrato socioeconómico; lo han padecido personajes conocidos, famosos, económicamente poderosos, intelectuales y artistas. El tratamiento del cáncer de cabeza y cuello ha sido motivo de controversia desde su descripción inicial hasta la actualidad. En la decisión terapéutica ha influido no solo el estadio del cáncer sino el entorno del paciente; en ocasiones, en un afán de disminuir la morbilidad derivada de los diversos tratamientos oncológicos, se han tomado decisiones erróneas que han implicado la pérdida de la vida del enfermo. Infortunadamente, en la actualidad seguimos viendo estas conductas. Se presenta una síntesis de casos de connotados personajes que presentaron este cáncer y se describe el impacto que ello implicó en la sociedad de ese momento.

PALABRAS CLAVE: *Epidermoide. Carcinoma. Cabeza. Cuello. Historia de la medicina.*

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Introduction

Squamous cell carcinoma originating in the mucous membranes of the head and neck is the most common malignant tumor in that area. It is considered a health problem, given that it affects working-age people. Sometimes, the sequelae of treatment or of the neoplasm itself are devastating for the individual and can make it difficult, and even impossible reintegrating the patient to his/her socio-economic environment.[1]

Despite progresses in the knowledge of the biology and prognostic factors of this neoplasm and advances in diagnostic and therapeutic methods, mortality continues to be high due to a delay in its identification: 500,000 new cases are estimated to be diagnosed annually in the world, 60 % at locoregionally advanced stages, which implies an approximate 5-year survival of 50 %.[2-4]

Squamous cell carcinoma of the head and neck has been known since time immemorial, and although there is evidence of this condition since the pharaonic era, it was not paid attention to until five celebrities suffered from it at different times in history: Emperor Frederick III of Germany, US presidents Ulysses Simpson Grant and Grover Cleveland, Sigmund Freud and the famous musician and operatic composer Giacomo Puccini, who due to this condition left the Turandot opera unfinished. This is how efforts for early recognition of this cancer and the search for the best therapeutic alternative began.

Historical background

The earliest traces of head and neck carcinoma were found in Egyptian mummies dating back 5000 years B.C.; at least three cases of nasopharyngeal cancer (endemic in the area to date) and three cases of maxillary osteosarcoma have been identified in them.

In the Ebers Papyrus, written in the time of Amenophis I, early in the 16th century B.C., the case of a cancer in the mucosa of the lower gum that was treated with tumor ablation using a red hot metallic instrument is described. Numerous tracheotomies are also described for the management of tumors that blocked the airway. In the 1st and 2nd centuries, the Greeks Celso and Galen reported various carcinomas on the lip and tongue. In addition, skulls with lesions in the paranasal sinuses have been found in excavations from the time of imperial Rome dating from the 1st to 3rd centuries of our era.

Despite these descriptions and findings, head & neck cancers went unnoticed and were little mentioned in history, until the personalities that motivated our paper were diagnosed with this disease.[5,6]

Prince Frederick larynx cancer

Frederick III of Hohenzollern, last Emperor of Prussia, a heavy pipe smoker, heir to the throne for 27 years, finally succeeded his father as King of Prussia and German Emperor in March 1888. In 1871, supported by Chancellor Otto von Bismark, he created the Second Reich and favored the German unification and the adhesion of the Imperial Territory of Alsace and Lorraine in a lavish ceremony held in the gallery of mirrors of the Palace of Versailles.

In January of 1887, being the first in the line of succession to the throne and with 56 years of age, he suffered a cold that caused dysphonia, which was looked after until March of that year. Professor Gerhardt, who performed the clinical examination, identified a “polypoid lesion in the left vocal cord”, for which he prescribed symptom treatment, without improvement. Two months later, doctors van Bergman and Todd suggested a laryngofissure (medial thyrotomy) to perform a biopsy on suspicion of laryngeal cancer. The prince’s physician, Dr. Wegner, Princess Victoria and Queen Victoria, (Prince Frederick’s wife and mother-in-law) leaned towards the opinion of Dr. Morell Mackenzie, a famous English laryngologist,[7] who ruled out the existence of cancer and diagnosed “laryngeal syphilis”. A biopsy of the lesion was taken by direct laryngoscopy and was evaluated by the famous histopathologist Rudolf Virchow,[8] who reported pachydermia; treatment continued to be symptomatic.

Due to the worsening of the condition, another biopsy was performed, which was again negative for cancer. Dr. Mackenzie instituted treatment with iron chloride baths; however, the dysphonia was increasing and data consistent with respiratory distress appeared. In June, the doctors palpated a cervical adenopathy; despite the evidence, Mackenzie still denied that it was laryngeal cancer, and the condition was left to evolve freely. In February 1888, 13 months after the onset of dysphonia, the prince had to undergo emergency tracheotomy. The procedure was bloody; the doctors had to insert their fingers across the tumor to open the trachea; there was transoperative bleeding and Prince

Frederick almost died. As a sequel of the surgery, a cervical and peristomal abscess was formed, which persisted until the ruler's death.

On March 9, 1888, Emperor William I of Germany died and Frederick III ascended to the throne. People on the streets chanted "the emperor is dead, long live the dying emperor". In the days following his coronation, the new emperor expelled tumor fragments through the tracheostomy stoma, which were analyzed by Waldeyer and only thus the histological result, squamous cell carcinoma of the larynx, was obtained. Despite the evidence, Mackenzie continued to support his laryngitis diagnosis. Progression of the condition was accelerated and the tracheostomy cannula was repeatedly blocked by tumor fragments, which caused severe respiratory distress. Finally, in June 1888, 17 months after the onset of dysphonia, the emperor died due to massive hemorrhage caused by the tracheostomy. Frederick III is known as "the 99-day emperor".

The death of the emperor implied a disaster for Germany and for the world. Frederick III was a liberal; however, his successor, his son William II, who was authoritarian and impulsive, blocked the pacifist policy of Chancellor Otto von Bismarck and encouraged the conflict that led to World War I, which cost 2 million deaths to Germany and 10 million to the world, and where 70 million human beings were mobilized to the front lines.

The first total laryngectomy had been described in 1874 by Billroth. In France, the first series of laryngectomized patients was detailed by Labbé in 1885. The technique had been described by both these authors and by Gluck in Germany, by Périer in France and by Tapia in Spain, and thus the way to proceed in laryngeal cancer was known. Management was probably conservative, since mortality within the first week after total laryngectomy was 40 %, with a survival of only 8.5 %, as reported in a series of 103 laryngectomies published by Wolfender in 1887. The case of the emperor focused the attention on timely diagnosis, initial symptoms, the causes of the neoplasm and the mistakes made in diagnosis and treatment.[9,10] Paradoxically, these errors regarding laryngeal cancer are still observed to date.

General Grant and oropharyngeal cancer

Ulysses Simpson Grant is a very popular general in the United States because he was chief of staff of the Union troops in the Civil War, and because his victory over General Lee brought peace to that nation. A heavy cigar and cigarette smoker since the age of 23, he was elected 18th president of his country in 1869.

In June 1884, seven years after having completed his term as president, he complained of odynophagia and in October of that year, doctors de Acosta and Douglas issued the diagnosis of cancer of the oropharynx. The tumor invaded the tonsil, the palatine veil and the base of the tongue, onto which it was fixed; it was accompanied by bilateral lymphadenopathy in the neck. Transmandibular oropharyngectomy was proposed; however, after reassessment, the procedure was discarded. The general retired to write his memoirs and nine months later died, amidst economic ruin, neuropathic pain, periods of asphyxia and constant hemorrhages from the oral cavity.

Transmandibular oropharyngectomy was described by General Grant's treating physicians: Sands, Douglas and Shadry; however, due to hemorrhage, surgical wound infections and to the advanced stage, the procedure was not performed. In France, transmandibular oropharyngectomy was reported in 1906 by Vallas and Latarjet, but it was Dargent, in 1952, who obtained better results with a careful patient selection. Finally, the procedure was popularized in the 1950s by Hayes Martin in New York, who called it a COMMAND operation, due to the type of combined access (oral and cervical), which reminded the Canadian commands in the battle of Dieppe in then recently concluded World War II.[10-12]

President Grover Cleveland and cancer of the oral cavity, hard palate subsite

Grover Cleveland –a lawyer, member of the Democratic Party and considered the father of financial orthodoxy– was elected as the 22nd President of the United States in 1884. At the beginning of his second presidential term, he noticed a lump on the hard palate, which prompted him to seek medical help. His case exemplifies the importance of timely diagnosis, adequate treatment and the importance of oral cavity tumors resection.

When Dr. O'Reilly, the White House doctor, saw the lesion, he took a biopsy that was secretly submitted for analysis; the report indicated invasive squamous cell carcinoma. The president feared that making the diagnosis public would unleash financial panic on Wall Street; therefore he decided to be treated in secret. The large hall of a private yacht anchored in New York was adapted as an operating room. Due to the president's

corpulence and short neck, anesthesia had to be combined with nitrous oxide and local cocaine injections. The resection encompassed from the first premolar to the intermaxillary region, lasting one hour and 45 minutes; the postsurgical cavity was plugged with a iodine wick. The surgery was carried out by Dr. Joseph Bryan, who had published a review of 250 maxillectomies (out of which only two had been performed by him). Evolution was adequate and a rubber prosthesis perfectly sealed the site where the surgery was performed, which allowed adequate swallowing and language articulation. The president died 15 years later from other causes, without ever having experienced a relapse.

President Grover Cleveland's disease was made public in 1917, and thanks to its good evolution, the treatment, follow-up and rehabilitation of patients undergoing this type of interventions were given importance.[10-14] In 1980, the case was reevaluated and it was concluded that it had been a verrucous carcinoma of the hard palate, which explains the good prognosis with a single therapeutic variety.[15]

Giacomo Puccini

Giacomo Antonio Domenico Michele Secondo Maria Puccini, the famous Italian composer, was born in 1858 in Luca, in Tuscany, Italy. He has been considered the greatest opera composer of the late 19th and early 20th centuries. His famous works include *Manon Lescaut*, *La Bohème*, *Tosca*, *Madame Butterfly* and *Turandot*, with the latter being left unfinished due to the progression of the author's laryngeal cancer.[16]

Puccini, an intense cigarette and cigar smoker, consulted with different otolaryngologists in February 1924 for dysphonia, otalgia, dysphagia and odynophagia. The diagnosis was "rheumatic inflammation of the throat", for which he received symptomatic treatment. In November of that year, he noticed weight loss, increased otalgia and that he was unable to close the shirt collar due to cervical lymph nodes growth. In Florence, Torregiani diagnosed him with "supraglottic extrinsic cancer of the size of a nut". In those days, laryngeal carcinomas were classified as intrinsic (with slow evolution and good prognosis) and extrinsic (with palpable lymph nodes in the neck, aggressive and of poor prognosis, with the recommendation therefore being to leave patients to evolve freely). A biopsy confirmed squamous cell carcinoma.[10,16]

There are several situations that influenced the treatment decision that was made with Puccini: his quality as a noted musician, the morbidity total laryngectomy entailed in those days, the uncertainty that he would benefit from conservative laryngeal surgery and the advent of a novel treatment, radiation, which was chosen in order to avoid mutilation. Puccini went to Brussels, where the only European center that offered radiation was located.[17] Ledoux started treatment with a "necklace that contained radius", about which Puccini complained: "they are crucifying me like Christ. I have a necklace around the throat with radiation in it; it is torture".

A few days later, under local anesthesia, Ledeux inserted seven needles with radiation in the composer's neck, performed a tracheostomy and placed a nasogastric tube; the procedure took three hours. Regarding his condition, Puccini wrote: "I feel like I have bayonets in my throat. This is horrible!" Four days later, Puccini had a terminal hemorrhage from the mouth and tracheostomy, and died on November 29, 1924, at dawn, which reminds of the finale of his aria *Nessun Dorma*, when Prince Calaf sings *All'alba, vincerò!*

Puccini died without concluding the opera *Turandot*, thus depriving humanity of a surely extraordinary "finale". *Turandot* last two scenes were finished by Franco Alfano under the supervision of Arturo Toscanini. The night of the premiere at *La Scala*, Toscanini himself, who directed the orchestra, interrupted the performance where the *maestro* had left the composition, turned to the audience and said: "This is where the opera concludes, because here is where the *maestro* died".

The composer popularity and the therapeutic novelty of the moment, radiation, influenced on total laryngectomy and neck dissection not being performed as it was indicated, even though the technique had been described more than three decades earlier and there was enough experience.[10,16,18] The wrong therapeutic decision was probably based on various factors other than the extent of the neoplasm. Even today, in locoregionally advanced neoplasms, preserving the larynx is not the best decision, despite the therapeutic novelty of treating with chemotherapy and radiotherapy. With this treatment at its peak, mortality of patients with laryngeal cancer due to non-cancer-related causes has been reported to have increased, perhaps due to treatment-associated complications.[19]

Sigmund Freud and cancer of the oral cavity and central facial skeletal structures

Of Austrian nationality, born in Moravia, father of psychoanalysis and a heavy, regular consumer of cigars, Freud had a tumor on the hard palate discovered

at 67 years of age. He was evaluated by Dr. Majek, who tried to resect the tumor,[20] but the procedure had to be interrupted due to major bleeding. Only a biopsy was obtained, which revealed a squamous cell carcinoma. Radiation therapy was advised, given the "non-resectable" nature of the tumor, which persisted despite radiation. Dr. Pischler initially performed an external carotid ligation, lymph node resection and large resection of the oral cavity in the area of the intermaxillary region and the palatine veil; the defect was occluded with a forearm graft.[21]

In addition to complementary radiotherapy, Freud was advised to have vasectomy performed in order to "slow down aging". After radiotherapy, a palatal rubber obturator was placed, which was repeatedly adjusted to the surgical cleft. Over the ensuing 13 years, Freud underwent 32 operations with the purpose to resect carcinoma foci on the palate and maxillary remnant; he suffered a destruction of the central facial skull, both by the tumor and due to cocaine habitual consumption.[22] Finally, he had massive tumor progression to the central facial skull and oropharynx, which caused his death in 1939.

Although a 13-year survival was achieved in Freud, the neoplasm never disappeared. Again, we are faced with different non-cancer-related factors that influence on therapeutic decisions. With radical maxillectomy, which was described by Genzoul in France since 1827, radical excision of the tumor would probably have been achieved, along with adequate control. Ferguson had even already replaced the original transoral with the transfacial route (still in use today). This approach was never tried in Sigmund Freud, without the reason for that decision being known.[10]

The impact of head & neck cancer on other celebrities in history

The celebrities mentioned bellow had head & neck cancer; some of them were subjected to medical malpractice. Many other celebrities have died due to this neoplasm, although the impact of this fact on the development of humanity has not been as transcendent as in the referred cases. Some of the most renowned include the following:

- John Steele, paratrooper of the 82nd Airborne Division, who, when being dropped during Operation Overlord in 1944 (the Normandy landings), had his parachute caught in one of the pinnacles of the Saint Mère Eglise church tower, leaving him hanging. He saved his life by not being able to participate in the battle, where most of his comrades died. Years later, in 1969, he died of laryngeal cancer.
- Lana Turner, American actress, famous for countless films, especially *The Postman Always Rings Twice*, died in 1992 from cancer of the hypopharynx and cervical esophagus.
- Sylvia Kristel, an actress who was native to Utrecht, the Netherlands, icon of erotic cinema of the 1970s and 1980s for the movie *Emmanuelle*, died in 2012 due to oropharyngeal cancer related to heavy smoking.
- Jack Klugman, recognized for playing the leading character of the TV series Dr. Quincy, died of laryngeal cancer in 2012.
- Rusell Means, known for his role in the movie *The Last Mohican*, perished in 2012 due to oral cancer (tongue).
- René Houseman, who was soccer world champion with the Argentina national team in 1978, died of tongue cancer in 2018.
- Juan de Borbón, father of the emeritus king of Spain, Juan Carlos de Borbón, died of laryngeal cancer.
- Prince Tomohito, in the line of succession of the Japanese Empire, died of supraglottic laryngeal cancer associated with alcoholism.
- Aldous Huxley, British writer, famous for his novel *A Brave New World*, died of laryngeal cancer.
- William Hanna, producer of *The Flintstones* among other cartoon series, died of laryngeal cancer.
- Jack Hawkins, a British actor famous for his performance in *Land of the Pharaohs* and *Lawrence of Arabia* and remembered as Quintus Arrius in the 1959 *Ben-Hur* movie, died of laryngeal cancer.
- Katharine Hepburn, actress, died of oropharyngeal cancer.
- Ed Sullivan, famous for conducting the television show that had his name and where he presented the Beatles for the first time in America, died of oropharyngeal cancer.
- George Harrison, member of the Beatles and heavy smoker, developed two primary tumors, bronchogenic and larynx; complications of the latter ended his life.
- Sammy Davis Jr., actor, died of laryngeal cancer.
- Babe Ruth, a regular cigar smoker, died of oropharyngeal cancer. He set a record for home runs in the major baseball leagues in 1935, a record that was broken until 1974 by Hank Aaron.

– Henry of Prussia, son of Frederick III, just like his father died of laryngeal cancer associated with the intense habit of smoking tobacco.
– Tito Vilanova, coach of the Barcelona Soccer Football Club, died of parotid cancer.

In recent years numerous public figures have been diagnosed with squamous cell head and neck cancers, although they have survived them:

– Michel Douglas, who, after to the proper management of his oropharyngeal cancer, controlled with chemotherapy and radiotherapy, has become an activist for the timely detection of this neoplasm.
– Edie van Halen, rock performer, had tongue cancer.
– Bruce Dickinson, vocalist of the Iron Maiden rock group, had tongue cancer.
– Charlie Watts, drummer for The Rolling Stones, had laryngeal cancer.
– Val Kilmer, who played the protagonist of one of the Batman movies, had laryngeal cancer.

Conclusion

Currently, head & neck cancer ranks sixth among all neoplasms. In Mexico, 60 to 70 % of patients are diagnosed at advanced stages, in which 5-year survival hardly exceeds 50 %, even with all therapeutic resources available. The causes of this include patients' lack of knowledge about their risk factors, underestimation by patients themselves of incipient symptoms and signs such as dysphonia, mouth ulcers or oral bleeding and lack of knowledge of primary care doctors about the warning signs that are indicative of immediate referral to the specialist.

Survival improvement is achieved, as in other neoplasms, not with more radical or expensive treatments, but with diagnosis at early stages and implementation of a therapeutic approach (even non-radical), which offers better oncological control and survival.

Despite being widely known, as I have described, mistakes are still being made in this neoplasm in terms of diagnosis and treatment, as it occurred to Emperor Frederick III of Prussia and Giacomo Puccini.

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ORIGINAL ARTICLE

Neurological repercussions of changes in cerebral blood flow in neonates undergoing cardiovascular surgery

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Abstract

Introduction: *Surgery for congenital heart disease can generate cerebral perfusion-associated alterations with neurological repercussions.* **Objective:** *To analyze the relationship of peri-surgical cerebrovascular resistance index (RI) with mediate neurological functions after congenital heart disease surgery.* **Method:** *Prospective cohort study of 34 neonates in whom basilar artery RI, serum oxygen, carbon dioxide and lactate levels were determined before and after palliative or corrective procedures. We related pre-surgical RI with post-surgical ability to initiate the enteral route or to restore unassisted spontaneous breathing.* **Results:** *Three groups were formed: 79 neonates with high RI (> 0.73), 73 with normal RI (0.63 to 0.73) and eight with low RI (< 0.63). In the former group, high RI persisted in the postoperative period, with persistent hyperlactatemia and hypoxia; in 86 %, the enteral route could not be initiated, and neither could assisted ventilation be withdrawn. In the second group, RI remained within normal values. In the third group, although RI, serum lactate and arterial oxygen pressure tended to normalize, 71 % had severe neurological damage.* **Conclusions:** *RI changes were common, although neurological damage appears to occur more commonly when RI remains high, possibly associated with low cerebral blood flow.*

KEY WORDS: *Resistance index. Cardiovascular surgery. Congenital heart disease. Neonate.*

Repercusión neurológica por cambios en el flujo sanguíneo cerebral en neonatos sometidos a cirugía cardiovascular

Resumen

Introducción: *La cirugía de cardiopatías congénitas puede generar alteraciones perfusorias cerebrales con repercusión neurológica.* **Objetivo:** *Analizar la relación del índice de resistencia (IR) vascular cerebral periquirúrgico con funciones neurológicas mediatas posteriores a cirugía de cardiopatía congénita.* **Método:** *Estudio de cohorte prospectivo de 34 neonatos en quienes se determinó IR de la arteria basilar, niveles séricos de oxígeno, dióxido de carbono y lactato, antes y después de procedimientos paliativos o correctivos. Relacionamos el IR prequirúrgico con la capacidad posquirúrgica para iniciar la vía enteral o restablecer la respiración espontánea no asistida.* **Resultados:** *Se integraron tres grupos: 79 neonatos con IR alto > 0.73, 73 con IR normal de 0.63 a 0.73 y ocho con IR bajo < 0.63. En los primeros persistió IR elevado en el posquirúrgico, con hiperlactatemia e hipoxia persistentes; en 86 % no se logró iniciar la vía enteral ni retirar la ventilación asistida. En los segundos, el IR se mantuvo en valores normales. En los terceros, si bien el IR, el lactato sérico y la presión arterial de oxígeno tendieron a normalizarse, 71 % presentó daño neurológico grave.* **Conclusiones:** *Los cambios en el IR fueron frecuentes, aunque el daño neurológico parece presentarse más cuando el IR se mantiene alto, posiblemente asociado con flujos cerebrales bajos.*

PALABRAS CLAVE: *Índice de resistencia. Cirugía cardiovascular. Cardiopatía congénita. Neonato.*

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Introduction

Therapeutic management, whether palliative or corrective, of neonates with complex congenital heart disease (CCHD) is a challenge due to high mortality and neurological sequelae.[1,2] The latter are attributed to hypoxic-ischemic events associated with cerebral blood flow variations. Although neurological damage might start since fetal life,[3,4] the highest risk is usually observed after birth, before or during heart disease corrective or palliative procedures.[5] Prior to this, neurological damage can be caused by CCHD-inherent chronic hypoxia, recurrent or persistent hypercapnia events or preoperative medications;[6-9] during cardiovascular surgery, it can be caused by the use of cardiopulmonary bypass.[10,11]

One determinant factor against hypoxic-ischemic damage is cerebral blood flow preservation by self-regulation of neuronal metabolic demands.[12] Pre-surgical hypoxia and blood volume variations during surgery can harm these mechanisms and facilitate neurological damage.[13] An indirect indicator of cerebral blood flow self-regulation functionality is the vascular resistance index (RI),[14] which is measured by transfontanellar Doppler ultrasound in cerebral arteries; among these, the basilar artery provides more information and allows the effect of perfusion to be assessed in basic survival areas.[15]

A neonate with CCHD without severe hemodynamic repercussion is expected to maintain a RI of between 0.63 and 0.73,[16] which does not occur if the malformation is not compensatory. In neonates with a history of moderate or severe asphyxia at birth, altered RI has been associated with neurological damage. In neonates with RI < 0.55 at between 36 and 72 hours after birth, greater subsequent neurological deterioration has been observed.[14] This has not been analyzed in neonates with CCHD undergoing cardiovascular surgery. The purpose of this work was to assess the effect of cardiovascular surgery on RI, as well as to analyze whether these changes affect early neurological functionality five days after the operation.

Method

Once approval of the local Research and Ethics Committee was obtained, with registration R 2015-3603-32, as well as informed consent of the children's parents, 34 patients attended to from October 2015 to May 2016 were recruited at the Pediatric Hospital of the National Medical Center *Siglo XXI*, Mexican Institute of Social Security, Mexico City. Neonates (< 28 days of life) with CCHD, scheduled for palliative or corrective cardiovascular surgery, were included. Children with multiple extracardiac malformations, children scheduled for therapeutic catheterization or without ultrasound record prior to surgery were excluded. Children who died during surgery were censored from the final analysis.

Pre-surgical medical treatments and scheduled surgery were decided by a group of neonatologists, cardiologists and cardiovascular surgeons, although the final surgical decision was determined based on trans-operative findings. Postoperative management was independent of the ultrasound study results and was based on the consensus of the doctors responsible for the child.

With pulsatile Doppler ultrasound (Hewlett Packard Sonos 5500® model with 8-MHz transducer), cerebral coronal sections were made in the anterior fontanelle until the basilar artery flow was located. The RI was obtained with the (systole-diastole)/systole formula, with the most acceptable pulse wave being measured and the maximum systolic peak velocity and end-diastolic peak velocity being obtained. The final value consisted of the average of three measurements made in 30 seconds. The measurements were always performed by a single trained evaluator and within a period not exceeding 45 minutes prior to the start of surgery. Two subsequent measurements were made, the first one at the conclusion of surgery and with at least 30 minutes of hemodynamic stability during intensive care unit stay; the second, at 18 hours. In addition, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2) and serum lactate (mmol/L) were determined at each time-point. Data on gestational age, birth weight, type of heart disease, age at the procedure, pre-surgical weight, RASCH-1,[17] use of analgesia or preload sedation, ventilatory support and enteral feeding were obtained from each patient. Regarding the performed procedure, data on cardiopulmonary bypass time, vascular clamping time and delayed or non-delayed closure of the sternum were recorded.[18]

To assess neurological functional condition after surgery, we recorded whether or not it allowed ventilatory support withdrawal and/or feeding initiation within the first five days following surgery. The decision on assisted ventilation withdrawal and feeding initiation was determined by the medical team based on clinical criteria (respiratory automatism, acid-base balance, soft abdomen with peristalsis and evidence

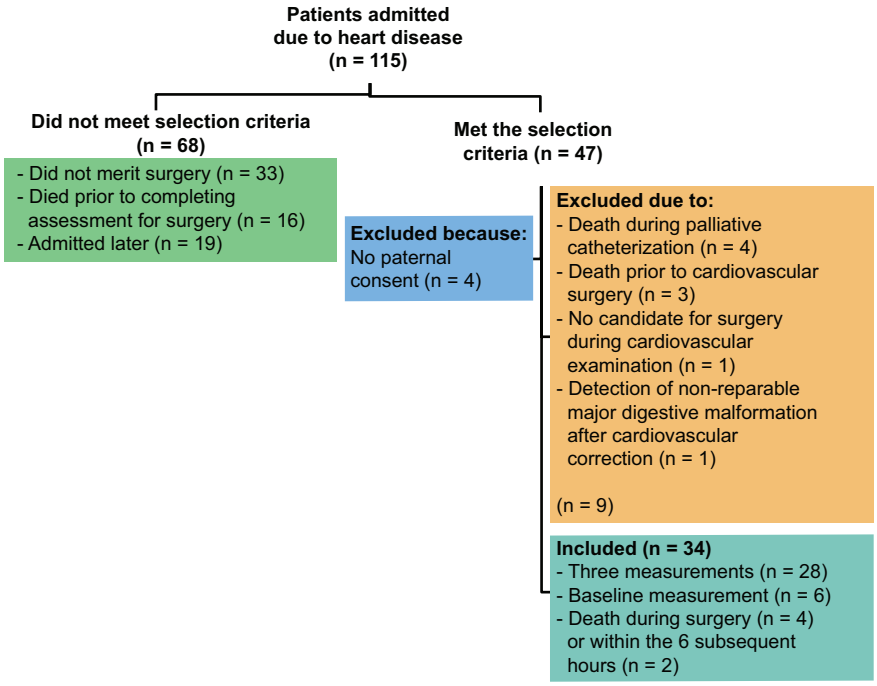

Figure 1. *Flow chart of the selection of neonates with complex congenital heart disease included in the study.*

of intestinal transit), regardless of the RI report and of researchers. Finally, survival to this admission period was determined.

Patients were grouped according to pre-surgical RI: normal, 0.63 to 0.73; low, < 0.63; high, > 0.73. Simple frequencies and percentages were obtained for categorical variables and medians with interquartile ranges for quantitative variables, given their abnormal distribution. To determine differences in the results at three specified time points, a non-parametric Wilcoxon test or the chi-square test was used. All analyses were performed with the statistical program SPSS, version 24. A p-value < 0.05 was considered to be statistically significant.

Results

As shown in Figure 1, 115 patients with CCHD were admitted, out of which 51 (42.8 %) met the selection criteria. Pre-surgical measurements were obtained in 34, and only in 28 were all three measurements available.

Demographic and clinical pre-surgery characteristics

Data are summarized in Table 1. Most neonates were males and full-term, with a median weight of 2900 g and 10 days of age at surgery. The most common heart disease was transposition of the large arteries, followed by abnormal connection of the pulmonary vessels. In nine, surgery was palliative, and in the rest, corrective; arterial switch was the most common (12/34; 35.2 %); 75 % of neonates received assisted ventilation, 50 % received sedative medication and 67 % were fasted. Adjusted surgical risk (RASCH-1) ranged from 1 to 6, and 61.7 % had a score of 3.

According to pre-surgical RI, seven patients (20.5 %) had normal values, eight (23.5 %) low and 19 (55.8 %) high.

Post-surgery evolution

Owing to their decease, six patients were not measured at all three scheduled time-points: four (11.7 %) died during cardiopulmonary bypass (two with high RI, one with normal RI and one with low RI), and two (5.8 %) in the immediate postoperative period, both with low RI, during the first hour of exiting cardiopulmonary bypass.

Delayed closure of the sternum was required by 21 (61 %) patients who survived the surgical procedure (Table 1). Two patients were operated on two occasions: in one case, pulmonary artery cerclage

Table 1. Clinical and demographic data of 34 neonates with complex congenital heart disease

Variable	Median	1, 3 quartile
Age at surgery (days)	10	2, 44
	Median	**Min-max**
Weight in grams at surgery	2900	1430-3835
	n	**%**
Male gender	22	64.7
Gestational age at birth		
< 37 weeks	4	11.8
≥ 37 weeks	30	88.3
Type of cardiovascular anomaly		
Transposition of large arteries	11	32.4
TLA + aortic coarctation/hypoplasia	2	5.9
Anomalous pulmonary venous connection	9	26.5
Aortic interruption/coarctation	3	8.8
Hypoplastic left ventricle syndrome	3	8.8
Pulmonary atresia	3	8.8
Single atrium and single ventricle	1	2.9
Ebstein anomaly	1	2.9
Atrioventricular canal	1	2.9
Pre-surgical management		
Analgesia	8	23.5
Sedation	17	50.0
Ventilatory support	25	73.5
Enteral nutrition	12	35.3
Performed surgeries		
Arterial switch	12	35.3
Systemic pulmonary fistula	8	23.5
Pulmonary vessels total repair	7	20.5
Aortic plasty	2	5.9
Norwood procedure	2	5.9
Pulmonary artery banding + aortic repair	1	2.9
Pulmonary artery banding	1	2.9
PVTR + ARP	1	2.9
RASCH-1 score		
1	1	2.9
3	21	61.8
4	10	29.4
6	2	5.9
Cardiopulmonary bypass time		
< 90 minutes	3	8.0
≥ 90 minutes	18	52.9
Clamping time		
< 60 minutes	8	23.5
≥ 60 minutes	13	38.2
Deferred sternal closure	21	61.8

TLA = transposition of large arteries, PVTR = pulmonary vessels total repair, ARP = aortic repair.

was initially performed and then corrective arterial switch, and in the other, initial aortic plasty and subsequent arterial switch (Fig. 1).

Post-surgery resistance index evolution

Figure 2 shows postoperative RI by groups. In patients with normal RI, there were no differences between their initial values (30 minutes) and 18 hours later (p = 0.223), in addition, the figures remained between 0.63 and 0.73 at all times. In children with low pre-surgical RI, it was normalized in the postoperative period: 0.65 at 30 minutes and 0.68 at 18 hours (Wilcoxon test p = 0.09). In neonates with high pre-surgical RI, it remained high: 0.82 at 30 minutes and 0.81 at 18 hours, p = 0.204.

O_2, CO_2 and serum lactate modifications in the post-surgical period

In all children, an increase in oxygen saturation was observed after cardiovascular surgery. The increase was more noticeable and constant in the group with low pre-surgical RI: 35, 45 and 65 mmHg in the measurements at baseline, at 30 minutes and at 18 hours (p = 0.007). The change was minimal in neonates with normal RI: 40, 61 and 57 mmHg for the same measurements (p = 0.738), as in those with high IR as well: 30, 46 and 50 mmHg (p = 0.014) (Fig. 3).

$paCO_2$ in neonates with low and high RI was reduced 30 minutes after surgery and was normalized at 18 hours: in children with low RI, measurements at baseline, at 30 minutes and at 18 hours were 36, 32 and 35 mmHg (p = 0.692); in those with high RI, 36, 32 and 36 mmHg, respectively (p = 0.19). The group with normal RI showed no changes: baseline, 36 mmHg, and at 30 minutes and 18 hours, 41 mmHg (p = 0.26) (Fig. 4).

Serum lactate was elevated since pre-surgical measurement in all patients. In those with normal RI, it did not change during the postoperative period: 3 mmol/L in the pre-surgical measurements and at 30 minutes, and 2.5 mmol/L at 18 hours (p = 0.554). In patients with low RI, it did increase at 30 minutes (2 to 4 mmol/L), and it remained high at 18 hours (4 mmol/L, p = 0.247). In the group with high RI, it increased from 2.5 mmol/L to 5.5 mmol/L at 30 minutes; at 18 hours, it dropped close to pre-surgical values (3.5 mmol/L, p < 0.0001).

Postsurgical clinical evolution

Postoperative neurological functionality was assessed in 28 patients (82.3 %). In 60.7 % (17/28), it was

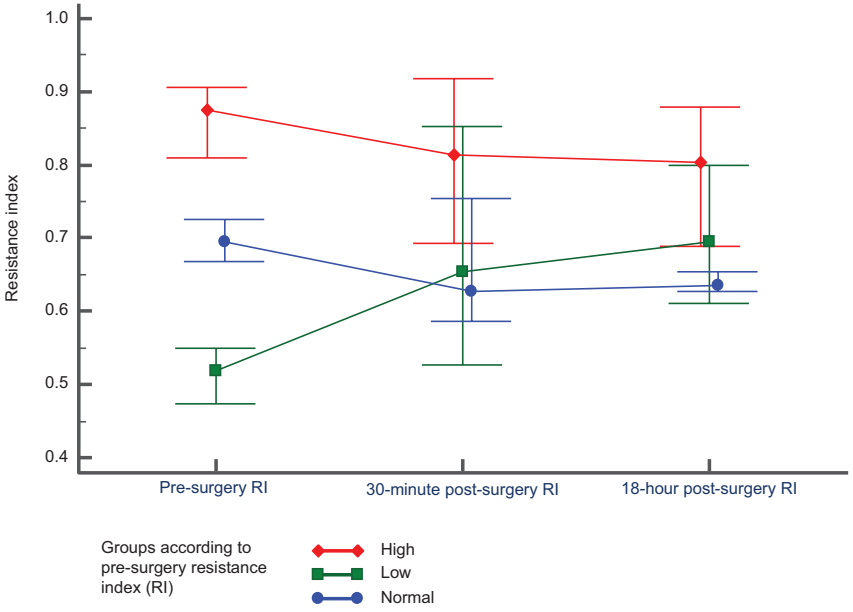

Figure 2. *Changes in resistance indices (RI) after surgery (30 minutes and 18 hours) according to pre-surgical values (normal RI, n = 5; low RI, n = 6; high RI, n = 17). The squares, circles and diamonds correspond to the medians, and the 'whiskers', to the 1-3 interquartile range. With Wilcoxon test, p = 0.091 was obtained for low RI, p = 0.223 for normal RI and p = 0.204 for high RI.*

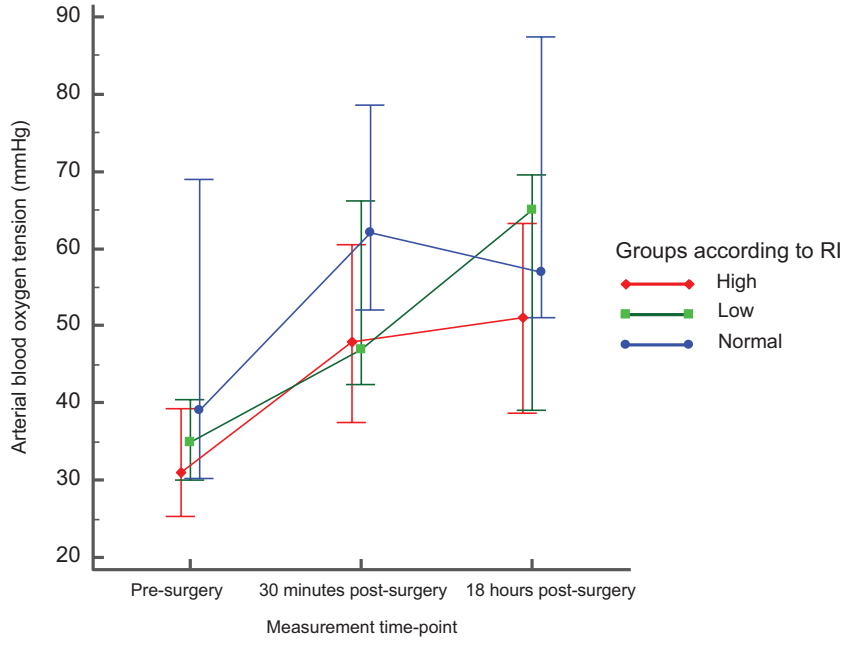

Figure 3. *Levels of arterial blood oxygen tension before and after the surgical procedure, according to the resistance index: normal, n = 5; low, n = 6; high, n = 17). The squares, circles and diamonds correspond to the medians, and the 'whiskers', to the 1-3 interquartile range. With Wilcoxon test, p = 0.007 was obtained for low RI, p = 0.74 for normal RI and p = 0.01 for high IR.*

unfavorable and did not allow enteral feeding initiation or assisted ventilation withdrawal within the first five postsurgical days (Table 2). A statistically significant difference between the groups could not be demonstrated. Only four patients in the high RI group (23.5 %) achieved complete neurological functionality.

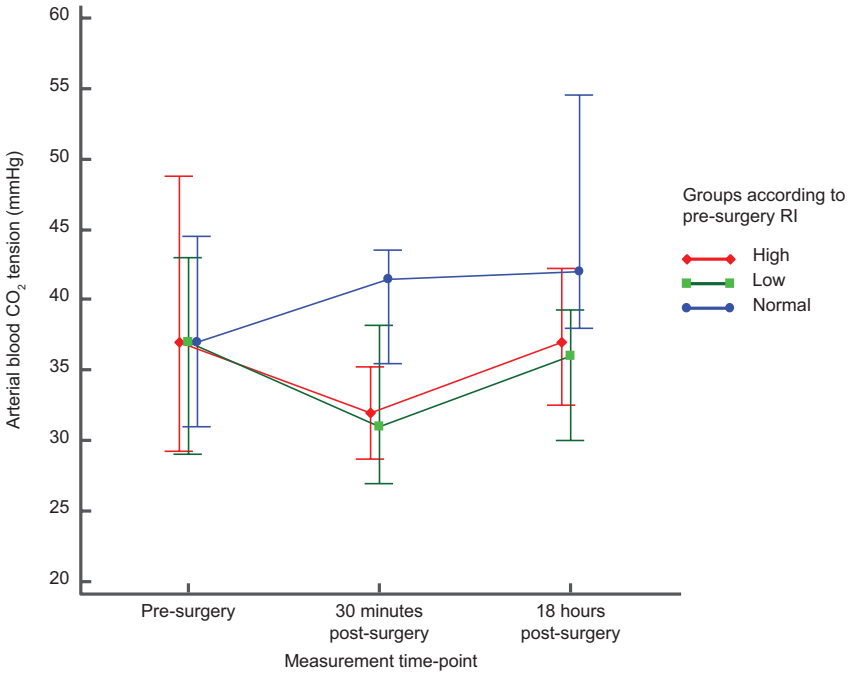

Figure 4. *Levels of arterial blood carbon dioxide tension before and after the surgical procedure, according to the resistance index (normal, n = 5; low, n = 6; high, n = 17). The squares, circles and diamonds correspond to the medians, and the 'whiskers', to the 1-3 interquartile range. With Wilcoxon test, p = 0.69 was obtained for low RI, p = 0.26 for normal RI and p = 0.13 for high RI.*

Table 2. Post-surgery neurological capabilities according to pre-surgery resistance index in 28 neonates with complex congenital heart disease

Neurological capability	Normal RI (n = 6)		Low RI (n = 5)		High RI (n = 17)		Total (n = 28)	p*
	n	%	n	%	n	%	n	
Not achieved for starting enteral nutrition or spontaneous breathing	4	57.1	4	50	9	47.3	17	0.35
Only start of enteral nutrition or spontaneous breathing	2	33.3	1	20	4	23.5	7	
Both enteral nutrition and spontaneous breathing achieved	0	0	0	0	4	23.5	4	
Death	2	28.5	4	50	5	26.3	11	

RI = vascular resistance index. normal RI, 0.63-0.73; low RI, ≤ 0.63; high RI, ≥ 0.73.
*Pearson's test, contingency coefficient = 0.34.

Discussion

An initial finding was that most patients (79 %) had a low or high RI prior to surgery, which implies a high prevalence of neonates with altered cerebral blood flow, possibly due to hemodynamic changes since the fetal stage and related to the heart defects.[19] It is possible that, with cardiovascular surgery, flows are redistributed and thereby the RI changes to normal levels within 18 hours after surgery, as it occurred in most patients. When cerebral blood flow is not normalized, there can potentially be neurological damage.[20]

On the other hand, due to the establishment of three different groups according to pre-surgical RI, it was possible to assess differential patterns in the vasculocerebral behavior secondary to the hemodynamic challenge a complex surgery implies. In the neonates with normal pre-surgical RI, a preserved cerebral vasomotor response was observed, with a slight increase in the RI at the conclusion of the surgical intervention, possibly owing to volume changes due to reperfusion after cardiopulmonary bypass withdrawal,[11] but which returned to normal value once the patient was stabilized at 18 hours.

In the group with a high presurgical RI, eight of the 19 patients had transposition of the large arteries or chronic hypoxic right heart failure, which are conditions that induce a RI increase; in these patients, despite a correction of the defect with an increase in partial pressure of oxygen, there was no vasodilation consistent with a substantial RI reduction, which can be explained by alterations in regional oxygen saturation.[20]

Contrary to our hypothesis that immediate postoperative period would be favorable in children with RI normalization, this only occurred in one patient with a previously elevated RI. Three other neonates with high pre-surgery IR also had a favorable postoperative period, but the RI values continued to be high. In the rest, it was difficult to decannulate or starting the enteral route or both.

Due to the small number of patients and the interaction of multiple factors, mainly the types of heart disease, it is difficult to analyze the conditions that affected neurological evolution. Particularly in neonates with low RI, although the values did increase during the postoperative period, subsequent evolution was very poor: three died and the others did not achieve respiratory and enteral autonomy. These findings are consistent with those observed by Ilves[21] in patients with severe asphyxia and explained as damage due to vasoparalysis secondary to delayed hyperperfusion. Perhaps in patients with high RI, cerebral self-regulation maintained better compensation for the changes in cerebral perfusion pressure.[15] When this self-regulation is impaired, efficacy depends exclusively on external factors such as blood pressure and blood volume, among others. We do not doubt that these mechanisms might have been abolished in the patients, with the conditions of surgical and anesthetic treatment contributing to it.[22]

Another contributing factor in several patients was the need to perform a delayed sternum closure. During the wait, they were under sedation, analgesia and intubation, which are high-risk conditions for new hypoxic-ischemic episodes.

Two important limitations of this study should be considered: one is the sample size, and the second, the follow-up period. Although it is difficult to reproduce the study due to the characteristics of the patients, a multicenter study will be necessary. Furthermore, vascular magnetic resonance imaging has been suggested as another option for peri-surgical assessment,[23] as well as analyzing other factors involved.[24]

Conclusions

A high proportion of patients with CCHD show cerebral RI alteration before the cardiovascular procedure, and although cardiovascular surgery appears to favor RI normalization, neurological repercussions could be already determined. In most patients, it was difficult to withdraw respiratory assistance or start enteral feeding due to inadequate central neurological control.

Acknowledgements

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ORIGINAL ARTICLE

Height and weight progression patterns in Mexican children aged between 6 and 12 years and differences with Ramos-Galván growth charts 40 years later

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Abstract

Introduction: *Children and adolescents weight and height are a reflection of the health status and socioeconomic development of a population.* **Objective:** *To evaluate height and weight progression patterns of Mexican children and compare them with Dr. Ramos-Galván growth charts 40 years later.* **Method:** *Cross-sectional survey conducted on the population of the National Physical Activation Program "Ponte al 100", which includes boys and girls aged six to 12 years.* **Results:** *43,670 boys and 44,103 girls were assessed, stratified by gender and age. The height progression pattern between six and 12 years was 21 cm in males and 22 cm in females, whereas the weight progression pattern was 9.86 and 10.05 kg, respectively, for males and females. The proportion of six- and 12-year-old boys who were overweight was 11.2 and 9 %, while 14.7 and 15 % were obese. The proportion of six- and 12-year-old girls who were overweight was 8.2 and 9.1 %, whereas 21.7 and 13.3 %, respectively, were obese. When the obtained values were compared with those of Dr. Ramos Galván growth charts for boys and girls, the average difference was 2 cm.* **Conclusions:** *No secular height or weight increase within the last 40 years was documented.*

KEY WORDS: *Weight. Height. Growth charts. Growth. Secular height increase.*

Progresión de talla y peso en niños y niñas entre los 6 y los 12 años y su diferencia con las tablas de Ramos Galván 40 años después

Resumen

Introducción: *El peso y la talla de niños y adolescentes son un reflejo del estado de salud y desarrollo socioeconómico de la población.* **Objetivo:** *Evaluar las progresiones de talla y peso de niños y niñas mexicanos y compararlas con las tablas del doctor Ramos Galván a 40 años de distancia.* **Método:** *Encuesta transversal realizada en población del Programa Nacional de Activación Física Ponte al 100, que incluye niños y niñas de seis a 12 años.* **Resultados:** *Se evaluaron 43 670 niños y 44 103 niñas, que se estratificaron por sexo y edad. La progresión de talla entre los seis y 12 años fue de 21 cm en hombres y de 22 cm en mujeres; la progresión de peso fue de 9.86 y 10.05 kg, respectivamente para hombres y mujeres. La proporción de niños de seis y 12 años con sobrepeso fue de 11.2 y 9 % y con obesidad, de 14.7 y 15 %. La proporción de niñas de seis y 12 años con sobrepeso fue de 8.2 y 9.1 % y con obesidad, de 21.7 y 13.3 %, respectivamente. Al comparar los valores*

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obtenidos con los de las tablas del doctor Ramos Galván para niños y niñas, el promedio de diferencia fue de 2 cm. **Conclusiones:** *No se documentó un incremento secular de la talla ni del peso en los últimos 40 años.*

PALABRAS CLAVE: *Peso. Talla. Tablas de crecimiento. Crecimiento. Incremento secular de la talla.*

Introduction

While modernization and globalization in developing countries is partly responsible for social and economic problems, it has also brought significant improvements in the quality of life such as increased access to and distribution of food, urbanization, education and health, which have resulted in a reduction in children morbidity and mortality and nutritional improvement.[1-4] Portugal refers a height increase of 5.7 cm in 40 years,[5] and in some Latin American countries there has been a 9-cm increase in final adult height.[6 7]

Medical care of the healthy child is based on the monitoring of height and weight. In Mexico, the last height standardizations were carried out by Dr. Ramos-Galván in 1975, with a predominance of children from Mexico City, who had great nutritional advantages in relation to the rural population.[8,9] Similarly, the height and weight charts of the Centers for Disease Control (CDC) of the United States, published in 2000, have been recommended.[10] The purpose is to have updated parameters for the follow-up of the healthy Mexican child and to determine whether in the Mexican population there has been an increase in height over the last 40 years, considering rural and urban areas.[11,12]

Methods

The present study is a secondary analysis of *Ponte al 100*,[13] a national intervention program carried out in elementary and secondary public schools in Mexico, where a regime of physical exercise and diet is individually prescribed. An informational meeting is held at each participating school, voluntarily attended by students, parents and teaching personnel. Teachers who agree to participate as evaluators take a course where they are instructed on the use of anthropometric and functional capacity measurement techniques, as well as on the recording of data in a computer platform. Students whose parents or legal guardians agree to participate by signing the corresponding informed consent document undergo an initial evaluation that includes the following:

- Registration of demographic data (age, gender, place of origin and residence).
- Anthropometry and body composition (weight, height, body mass index, percentage of body fat and lean mass, waist, hip and arm circumference).
- Motor fitness (muscular strength and flexibility of the arm, leg and abdomen).
- Musculoskeletal fitness (balance, speed and agility).
- Cardiorespiratory fitness (maximum oxygen consumption during a 20-m run test).
- Neuropsychological fitness (memory and attention assessed by a standard memory challenge test).

So far, the program has enrolled more than one million children and adolescents, and data on the outcome of the nutritional and exercise intervention are currently being analyzed. For this study, demographic and body composition data taken during the initial evaluation were used. Children with any known disease were excluded, as well as those who chronically used medications, or who were in a special nutrition program or who showed any alteration in the measurement of vital signs at rest, which, in that case, were referred to the local health center to receive medical attention.

Height in the standing position was measured with a portable stadiometer in accordance with standard anthropometric guidelines, with the participant standing in the Frankfurt plane. Total weight and body fat percentage were determined by bioelectrical impedance analysis (Tanita UM-081®, Tanita International Division, UK). The body mass index was calculated using the weight/size formula.[2] These data are stored in a computer platform where each participant can only access their own data through a username and password. Only members of the *Ponte al 100* team have access to the data of all participants, in compliance with the confidentiality laws.

The *Ponte al 100* project was approved by the Research and Ethics Committee of the American British Cowdray Medical Center of Mexico City.

Mean height and weight for each age group were calculated with their standard deviation and range. Based on these values, growth curves for gender and age were generated. Finally, the height for gender means were compared with those recorded in the charts created by

Dr. Ramos-Galván in 1975 and the CDC charts of 2000 using a network meta-analysis for cross-sectional studies,[14] for weighted means with random effects; the Cochrane Collaboration RevMan 5 program was used. The results were represented using forest plots with mean differences and 95 % confidence intervals.

Results

Anthropometric data of 43,670 boys and 44,103 girls aged between six and 12 years were analyzed. Tables 1 and 2 show the mean values of height in meters (Fig. 1), weight in kilograms, body mass index (BMI), fat percentage, waist circumference in cm and the classification in overweight and obesity according to the CDC criteria.

The progression of height from six to 12 years was 21 cm in males (1.20 ± 0.10 to 1.41 ± 0.07) and 22 cm in females (1.19 ± 0.11 to 1.41 ± 0.07). The progression of weight was 9.86 kg in males (25.62 ± 6.87 and 35.48 ± 7.33) and 10.05 kg in females (25.42 ± 6.63 to 35.47 ± 7.56). BMI progression was 0.8 kg/m^2 in males (17.1 ± 2.7 to 17.9 ± 2.8) and 0.4 kg/m^2 in females (17.4 ± 3.4 to 17.8 ± 2.8).

The percentage of body fat ranged from 16.03 ± 7.9 % to 18.79 ± 8.5 % in males and from 19.2 ± 7.2 % to 21.48 ± 7.0 % in females. Waist circumference in males ranged from 58.4 ± 8.02 cm to 68.18 ± 9.57 cm (difference of 9.78 cm) and from 58.5 ± 8.7 cm to 67.23 ± 9.1 cm (difference of 8.78 cm) in females.

The proportion of six- and 12-year-old boys with overweight was 11.2 and 9 % and with obesity, 14.7 and 15 %, respectively. The proportion of six and 12-year-old girls who had overweight was 8.2 and 9.1 %, whereas 21.7 and 13.3 % had obesity, respectively.

Height average difference in *Ponte al 100* school-age boys when making the comparison with Dr. Ramos-Galván charts (Fig. 2A) was non-existent, -0.02 m (-0.04, 0.01, p = 0.16); when the comparison was made with the CDC charts (Fig. 2B), the difference was -0.05 m (-0.07, -0.03, p <0.0001). For the girls, in the comparison with Dr. Ramos-Galván charts (Fig. 2C), the difference was, again, practically non-existent, although statistically significant: -0.02 m (-0.04, 0.00, p = 0.02); in comparison with the CDC charts (Fig. 2D), the difference was -0.05 m (-0.07, -0.04, p = 0.00001).

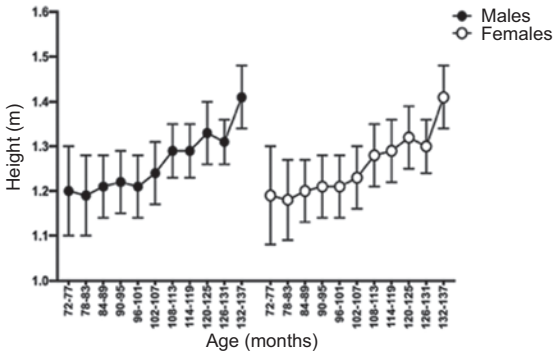

Figure 1. *Height measured in 43,670 boys and 44,103 girls. Height increase between 6 and 12 years of age was 21 cm in males (1.20 ± 0.10 to 1.41 ± 0.07) and 22 cm in females (1.19 ± 0.11 to 1.41 ± 0.07).*

Discussion

The weight and height progression profile of a population depends on various factors, both genetic and environmental.[15] At an individual level, height is genetically predetermined by biological systems functionality and integrity;[15] however, these systems depend on the nutritional and general health status of the individual. The secular height increase is a phenomenon where average height of a population increases depending on demographic and epidemiological transitions, with this phenomenon being a reflection of better health, nutritional and socioeconomic conditions.[16,17] Secular height increase during the 20th century is well documented in European and United States populations.[16-18] In Mexico, this phenomenon has been identified and characterized in urban and rural populations of Oaxaca.[19,20]

Our results at the beginning of school age (six years) show an increase of 4.5 cm in males (120 versus 115.5 cm) and 4 cm in females (115 versus 119 cm), which are larger than those referred to by the CDC charts of year 2000.[21] After seven years of age, these differences disappear: height is 5 cm larger in those referred by the CDC and practically the same to that referred by Dr. Ramos-Galván,[8] an thus there seems to be no significant gain over the last 40 years. From the point of view of height at seven years of age, our results are similar to those reported in other Latin American countries such as Colombia,[6] Venezuela[22] and Argentina,[23] although at 10 years of age in females and at 12 years in males it was lower. However, it should be noted that these series, particularly the Colombian, include only individuals of a high socioeconomic class, which undoubtedly influences on population growth and development.

The results above suggest that the height development pattern in healthy Mexican children is similar across the population and that it has not changed over

Table 1. **Growth charts for school-age boys**

Age, years (range in months)	*Ponte al 100** Mean ± SD (range)	Ramos-Galván* Mean ± SD (n)	CDC* Mean ± SD (n)	Weight, kg Mean ± SD (range)	BMI, kg/m^2 Mean ± SD (range)	% fat Mean ± SD	Waist circumference, cm Mean ± SD	Overweight, CDC %	Obesity, CDC %
6 years (n = 525) (72-77)	1.20 ± 0.10 (0.96-1.48)	1.14 ± 0.04 (60)	1.17 ± 0.05 (700)	25.62 ± 6.87 (16-47)	17.1 ± 2.7 (9.6-31.5)	17.05 ± 8.2	58.41 ± 8.02	11.2	14.7
6 years and 6 months (n = 1111) (78-83)	1.19 ± 0.09 (0.97-1.48)	1.14 ± 0.04 (60)	1.20 ± 0.05 (700)	24.25 ± 5.87 (15.2-47)	16.8 ± 2.9 (9.7-47)	16.88 ± 7.9	56.91 ± 7.19	9.7	8.8
7 years (n = 2538) (84-89)	1.21 ± 0.07 (1.05-1.40)	1.20 ± 0.04 (57)	1.23 ± 0.05 (700)	24.43 ± 4.71 (15.2-38.9)	16.5 ± 2.3 (8.5-32.2)	18.79 ± 8.5	57.42 ± 7.26	9.0	14.6
7 years and 6 months (n =4350) (90-95)	1.22 ± 0.07 (1.05-1.40)	1.23 ± 0.05 (57)	1.26 ± 0.05 (700)	24.74 ± 4.78 (15.1-38.9)	16.4 ± 2.2 (8.1-27.9)	18.45 ± 8.7	57.61 ± 7.47	9.1	13.8
8 years (n = 7071) (96-101)	1.21 ± 0.07 (1.07-1.40)	1.26 ± 0.05 (55)	1.29 ± 0.06 (700)	24.46 ± 4.89 (15.2-38.7)	16.4 ± 2.3 (8.6-30.3)	17.28 ± 8.5	57.41 ± 7.04	9.3	11.5
8 years and 6 months (n = 4339) (102-107)	1.24 ± 0.07 (1.07-1.40)	1.28 ± 0.05 (55)	1.32 ± 0.06 (700)	25.24 ± 4.89 (15.9-38.7)	16.3 ± 2.2 (8.1-28.9)	16.71 ± 8.5	57.90 ± 7.05	9.2	13.4
9 years (n = 5166) (108-113)	1.29 ± 0.06 (1.01-1.45)	1.33 ± 0.05 (52)	1.35 ± 0.05 (700)	28.55 ± 5.66 (17-43.3)	17.1 ± 2.6 (9.4-33)	17.33 ± 8.7	60.34 ± 7.77	9.1	13.6
9 years and 6 months (n = 2799) (114-119)	1.29 ± 0.06 (1.14-1.45)	1.33 ± 0.05 (52)	1.37 ± 0.07 (700)	28.1 ± 5.3 (16.3-43.3)	16.6 ± 2.2 (8.5-31.7)	16.51 ± 8.5	59.83 ± 7.04	9.2	12.2
10 years (n = 6799) (120-125)	1.33 ± 0.07 (1.17-1.49)	1.36 ± 0.06 (40)	1.40 ± 0.07 (700)	31.78 ± 6.82 (17.3-48.9)	17.8 ± 2.9 (9.0-33.9)	17.85 ± 8.6	62.88 ± 8.49	9.0	13.9
10 years and 6 months (n = 1179) (126-131)	1.31 ± 0.05 (1.17-1.45)	1.36 ± 0.06 (40)	1.42 ± 0.07 (700)	29.13 ± 4.82 (18-47)	16.9 ± 2.4 (9.8-28.2)	16.03 ± 7.9	59.97 ± 6.08	9.8	7.6
11 years (n = 7793) (132-137)	1.41 ± 0.07 (1.25-1.56)	1.41 ± 0.06 (34)	1.45 ± 0.07 (700)	35.48 ± 7.33 (19.5-54.6)	17.9 ± 2.8 (9.1-31.2)	17.58 ± 7.9	68.18 ± 9.57	9.0	15

*Height, m. SD = estimated standard deviation, CDC = Centers for Disease Control.

the last 40 years, either in Mexico City, as shown by Dr. Ramos-Galván charts more than 40 years ago, or in the rest of the country, as shown by our results, in which urban, suburban and rural populations are represented. Dr. Ramos-Galván charts included predominantly healthy children from Mexico City, which proved to be an adequate sample, since at that time it was the area of the highest socioeconomic development in the country, which guaranteed good nutrition and showed full height development. Forty years later, we can observe that average height development has reached its peak as a result of an improvement in access to food and health services throughout the Mexican territory.[24,25]

Table 2. Growth charts for school-age girls

Age, years (range in months)	*Ponte al 100* Mean ± SD (range)	Ramos-Galván* Mean ± SD (N)	CDC* Mean ± SD (n)	Weight, kg Average (range)	BMI, kg/m^2 Average (range)	% fat Mean ± SD	Waist circumference, cm Mean ± SD	Overweight (CDC) %	Obesity (CDC) %
6 years (n = 475) (72-77)	1.19 ± 0.11	1.14 ± 0.04 (118)	1.16 ± 0.07 (700)	25.42 ± 6.63 (16-48)	17.4 ± 3.4 (7.2-42.4)	19.5 ± 7.9	58.5 ± 8.7	8.2	21.7
6 years and 6 months (n = 1124) (78-83)	1.18 ± 0.09 (0.98-1.49)	1.17 ± 0.05 (118)	1.20 ± 0.05 (700)	24.05 ± 5.95 (15-48)	16.8 ± 3 (8.6-35.1)	19.2 ± 7.2	56.41 ± 7.24	9.4	9.6
7 years (n = 2473) (84-89)	1.20 ± 0.07 (1.04-1.40)	1.20 ± 0.05 (130)	1.23 ± 0.05 (700)	24.01 ± 4.84 (15.3-39)	16.4 ± 2.5 (8.8-31.4)	21.11 ± 7.3	56.92 ± 7.17	9.1	13.5
7 years and 6 months (n = 4362) (90-95)	1.21 ± 0.07 (1.04-1.40)	1.22 ± 0.05 (130)	1.26 ± 0.06 (700)	24.54 ± 5 (15.1-39)	16.5 ± 2.4 (9.6-35.1)	20.99 ± 7.3	57.47 ± 7.58	7.2	14.7
8 years (n = 6984) (96-101)	1.21 ± 0.07 (1.06-1.39)	1.25 ± 0.05 (152)	1.29 ± 0.06 (700)	24.07 ± 4.9 (15.5-38.2)	16.3 ± 2.3 (9.8-29.7)	19.96 ± 7.0	56.96 ± 7.10	9.2	11.8
8 years and 6 months (n = 4261) (102-107)	1.23 ± 0.07 (1.06-1.09)	1.28 ± 0.05 (152)	1.31 ± 0.06 (700)	24.84 ± 4.97 (16-38.2)	16.3 ± 2.3 (9.9-32.5)	19.77 ± 7.0	57.62 ± 7.08	9.2	12.9
9 years (n = 5259) (108-113)	1.28 ± 0.07 (1.13-1.53)	1.30 ± 0.05 (153)	1.34 ± 0.06 (700)	28.09 ± 5.58 (17-42.7)	17.0 ± 2.5 (8.8-32.8)	20.86 ± 7.2	59.99 ± 7.48	9.2	12.4
9 years and 6 months (n = 2918) (114-119)	1.29 ± 0.07 (1.13-1.53)	1.33 ± 0.06 (153)	1.36 ± 0.06 (700)	27.86 ± 5.31 (17-42.7)	16.6 ± 2.1 (8.8-29.9)	20.32 ± 7.1	59.43 ± 7.06	9.3	10.4
10 years (n = 6850) (120-125)	1.32 ± 0.07 (1.16-1.48)	1.36 ± 0.06 (143)	1.39 ± 0.07 (700)	31.27 ± 6.92 (17.2-48.3)	17.5 ± 2.8 (8.9-31.4)	21.48 ± 7.0	62.08 ± 8.2	9.0	15.0
10 years and 6 months (n = 1308) (126-131)	1.30 ± 0.06 (1.16-1.48)	1.39 ± 0.06 (143)	1.42 ± 0.09 (700)	29.08 ± 5.08 (18-48)	16.9 ± 2.6 (9.1-32.1)	19.7 ± 6.4	59.78 ± 6.5	9.7	8.0
11 years (n = 8089) (132-137)	1.41 ± 0.07 (1.23-1.57)	1.43 ± 0.07 (141)	1.45 ± 0.07 (700)	35.47 ± 7.56 (20-54.3)	17.8 ± 2.8 (9.9-32.7)	20.33 ± 7.0	67.23 ± 9.1	9.1	13.3

*Height, cm. SD = estimated standard deviation, CDC = Centersi for Disease Control.

It is important to highlight that our study population represents healthy school-age children from public schools across the entire country.[13] The prevalence of obesity found in this population at different ages (from 7.6 to 15 % in boys and from 8 to 21 % in girls) is similar to the prevalence reported in Halfway ENSANUT 2016, which clearly indicates the national representativeness of our study population.[26] The epidemiological transition shows the population shift from undernutrition to an adequate weight for age and height, but it is inevitably moving towards overweight and obesity. As the country's nutritional conditions continue to improve, a reduction in the incidence of overweight and obesity is expected to be observed as a result of an improvement in access to higher quality food,

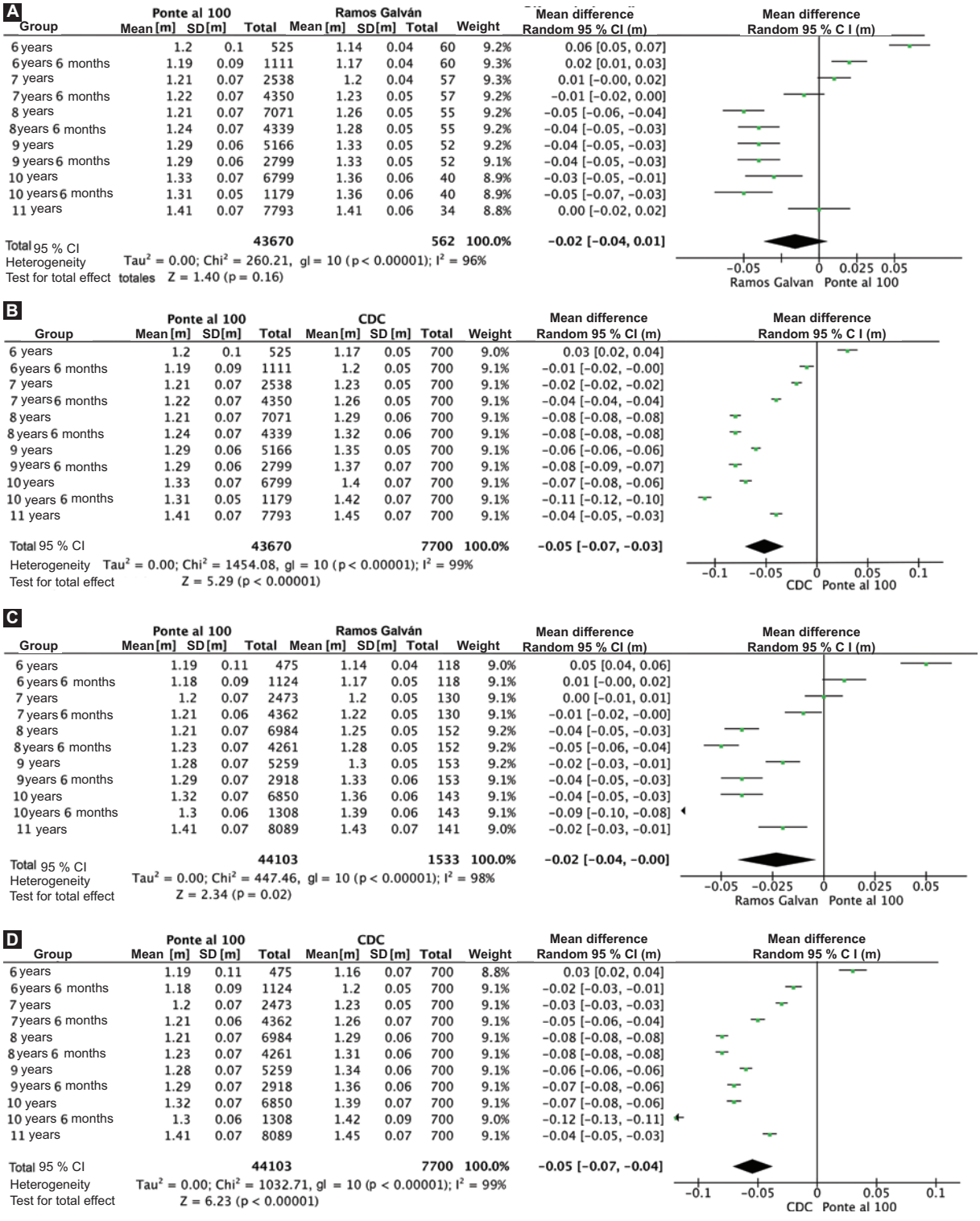

Figure 2. *Average height difference of school-age boys and girls enrolled in the Ponte al 100 program. A) Boys, -0.02 m (-0.04, 0.01, p = 0.16) in comparison with Dr. Ramos-Galván charts. B) Boys, -0.05 m (-0.07, -0.03, p < 0.0001) in comparison with the CDC charts. C) Girls, -0.02 m (-0.04, 0.00, p = 0.02) in comparison with Dr. Ramos-Galván charts, D) Girls, -0.05 m (-0.07, -0.04, p = 0.00001) in comparison with the CDC charts.*

accompanied by better physical activity habits, which are actions that are promoted by programs such as *Ponte al 100*.[13,27]

The limitations of our analysis include a possible variability in measurements as a result of the number of evaluators, although all had a similar level of

education and were standardized on the techniques. The advantages include the sample size, more than 87,000 boys and girls, which is why this is the largest anthropometric study in the world,[5,6,28-31] in addition to including all geographical areas and socioeconomic strata of Mexico.

Although the secular height increase over the centuries is a documented phenomenon,[17] in our study we failed to identify it. One explanation is that, as a species, we have reached maximum height, whose average remains stable due to access to food and health services optimization. Alternatively, there is the possibility that longer follow-up time is required to identify a true secular height increase.

There are multiple questions to be answered, including assessing if growth is more accelerated in obese children. The challenge as a country is and will continue to be, in the next few years, access to higher quality food and the development of physical activity habits that lead to an improvement in functional capacity and quality of life.[32-34]

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ORIGINAL ARTICLE

From ISET to InDRE. IV. Institute of Epidemiological Diagnosis and Reference: new orientation, 1990-2012

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Abstract

From 1990 to 2012, the Sanitary and Tropical Diseases Institute experienced the most important changes. In 1989, its name and orientation were modified to become the National Institute of Epidemiological Diagnosis and Reference. Shortly before, it had been formalized as the apex of the National Network of Public Health Laboratories and had incorporated laboratories for preventive programs such as exfoliative cytology and rabies, malaria and tuberculosis diagnosis; subsequently, it would incorporate other networks that emerged as part of the response to major epidemic outbreaks and to the new epidemiological outlook. In this period, 27 priority diagnostic algorithms were defined, organized in 18 networks, some of which began to collaborate with global networks. In 2001, the Institute started working with pathogens related to bioterrorism. By then, space restrictions of the headquarter's building were evident; in 2008, starting the construction of new facilities was decided. The Institute and its diagnostic networks constitute a milestone in Latin American public health of the 21st century.

KEY WORDS: *Sanitary and Tropical Diseases Institute. Institute of Epidemiological Diagnosis and Reference. History of medicine.*

Desde el ISET al InDRE. IV. Instituto de Diagnóstico y Referencia Epidemiológicos: nueva orientación 1990-2012

Resumen

De 1990 a 2012, el Instituto de Salubridad y Enfermedades Tropicales experimentó los cambios más importantes desde su origen. En 1989 modificó su nombre y orientación a Instituto Nacional de Diagnóstico y Referencia Epidemiológicos. Poco antes se había formalizado como cúspide de la organización piramidal denominada Red Nacional de Laboratorios en Salud Pública y había incorporado los laboratorios de programas preventivos como el de citología exfoliativa y los de diagnóstico de rabia, paludismo, tuberculosis; posteriormente incorporaría otras redes que surgieron como parte de la respuesta a brotes epidémicos importantes (cólera, VIH-sida, sarampión, influenza) y al nuevo panorama epidemiológico (dengue, Chagas, rotavirus). En este periodo se definieron 27 algoritmos diagnósticos prioritarios organizados en 18 redes, algunas de las cuales comenzaron a colaborar con redes globales. En 2001, en el Instituto se empezó a trabajar con patógenos relacionados con el bioterrorismo. Para entonces, las severas restricciones de espacio del edificio construido en 1935 fueron evidentes; en 2008, las autoridades decidieron iniciar el diseño y construcción de las nuevas instalaciones. En conjunto, el InDRE y sus redes diagnósticas constituyen un hito en la salud pública latinoamericana del siglo XXI.

PALABRAS CLAVE: *Instituto de Salubridad y Enfermedades Tropicales. Instituto de Diagnóstico y Referencia Epidemiológicos. Historia de la medicina.*

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Introduction

This article covers the 1990-2012 period of the Sanitary and Tropical Diseases Institute (ISET – *Instituto de Salubridad y Enfermedades Tropicales*), which was transformed into the National Institute of Epidemiological Diagnosis and Reference. The name was changed during the first quarter of 1989 and the collaboration between epidemiology and preventive programs was strengthened through the National Network of Public Health Laboratories (RNLSP – *Red Nacional de Laboratorios de Salud Pública*), which started operating at ISET in 1985.[1-3] An interaction of InDRE with international reference laboratories and global diagnostic networks was developed. The RNLSP also participated in the National Public Health Laboratory (now the Commission for Analytical Control and Coverage Broadening) as a reference for health surveillance of dairy, water and food.[4]

In 1997 and 2010, INDRE and RNLSP obtained regulatory support.[5,6] In 2000, as a result of the Law of National Health Institutes and without altering its new orientation, the term "National" was suppressed from the name of the Institute to become the Institute of Epidemiological Diagnosis and Reference (InDRE – *Instituto de Diagnóstico y Referencia Epidemiológicos*).[7] Only this denomination will be used.

During the study period, InDRE assumed the responsibility as a reference laboratory based on World Health Organization criteria: a specialized government laboratory that analyzes in depth the received samples; it advises, prepares, standardizes or evaluates diagnostic reagents; it issues guidelines for the operation of other laboratories, trains, conducts research and maintains relations with similar international centers.[8]

National Seroepidemiological Survey, a successfully overcome challenge

The National Seroepidemiological Survey forced the ISET to develop infrastructure and capacity to store, distribute and process half a million sera with their epidemiological information. The procedures were carried out with standard methods, under the control of international reference laboratories.[9] The results, published in 1992, established the baseline of these conditions in Mexico (Table 1).

The international situation

The epidemiological transition and the new global challenges positioned the public health laboratory.

Global initiatives such as the Rio Declaration on Environment and Development (1992) were carried out in the 1990s. The World Bank presented *Investing in health*, a report whose objective was to help improve the efficiency of the sector in low and middle-income countries (1993). The United Nations Millennium Goals initiative (1995) identified HIV/AIDS, tuberculosis, Chagas disease and malaria as priorities. Soon after, the World Health Organization made a balance of the global epidemiological situation, still characterized by a high mortality attributable to infectious diseases. By the end of the 20th century, it recognized the importance of chronic degenerative diseases and developed the Framework Convention for Tobacco Control. In turn, the World Heart Federation called the attention to the increase in cardiovascular conditions in countries of Latin America and Eastern Europe. In 2002, the World Health Organization launched the Global Strategy on Diet, Physical Activity and Health. In that year, the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria emerged; some resources were to be assigned to the InDRE.

The RNLSP for epidemiological diagnosis. Organization and integration process

Adolfo Pérez Miravete wrote:

> [In 1985]... the role the institution could play in the new organization of the Ministry was reviewed, and assigning it a new orientation in order to fulfill some perceived needs in epidemiological services was decided, particularly as an infrastructure for transmissible diseases surveillance services The organization of the National Network of Health Laboratories [sic] also required a national institution at the top of the pyramid organization.

With funds from the United Nations Program for Development,[10] between 1985 and 1989, the RNLSP responsibilities were reorganized, remodeled and strengthened.[11] The RNLSP organization is shown in Figure 1, where the vertical lines of the front face of the pyramid represent laboratory networks for mandatory diagnoses for all 32 public health state laboratories (LESP – *Laboratorios Estatales de Salud Pública*). The lateral face shows the diagnoses not organized by networks or mandatory that are carried out at InDRE with support from other levels. In the diagram, support and administrative processes are represented by horizontal lines. When they cross the technical procedures (vertical lines) they produce a grid with hundreds of checkpoints.

By 1992, the RNLSP was already structured in three levels: the federal level in charge of InDRE, the state

Table 1. **National Seroepidemiological Survey. Diagnoses made at ISET from 1987 to 1989**

Diagnosis	Tests (verified by international reference laboratory)	Number of samples* (age in years of the study population)	National prevalence Average (range)
Brucellosis	Plaque microagglutination (FAO/WHO)	66,982 (1 to 98)	3.42 % (0.24-13.5)
Toxoplasmosis	Indirect immunofluorescence (Canada)	29,279 (1 to 98)	32.0 % (17.1-66.5)
Chagas disease	Indirect hemagglutination Indirect immunofluorescence (Argentina)	66,678 (1 to 98)	1.6 % (0.1-5.0)
Measles	Hemagglutination inhibition (Mexico)	5,232 (12 to 59 months of age)	76.2 % (42.0-87.5)
Whooping cough	Microplate agglutination (United States)	25,666 (1 to 14)	61.8 % rural population, 68.5 % urban population

*Serum samples obtained on field work, urban and rural areas. FAO=Food and Agriculture Organization, WHO=World Health Organization.
Source: reference 9.

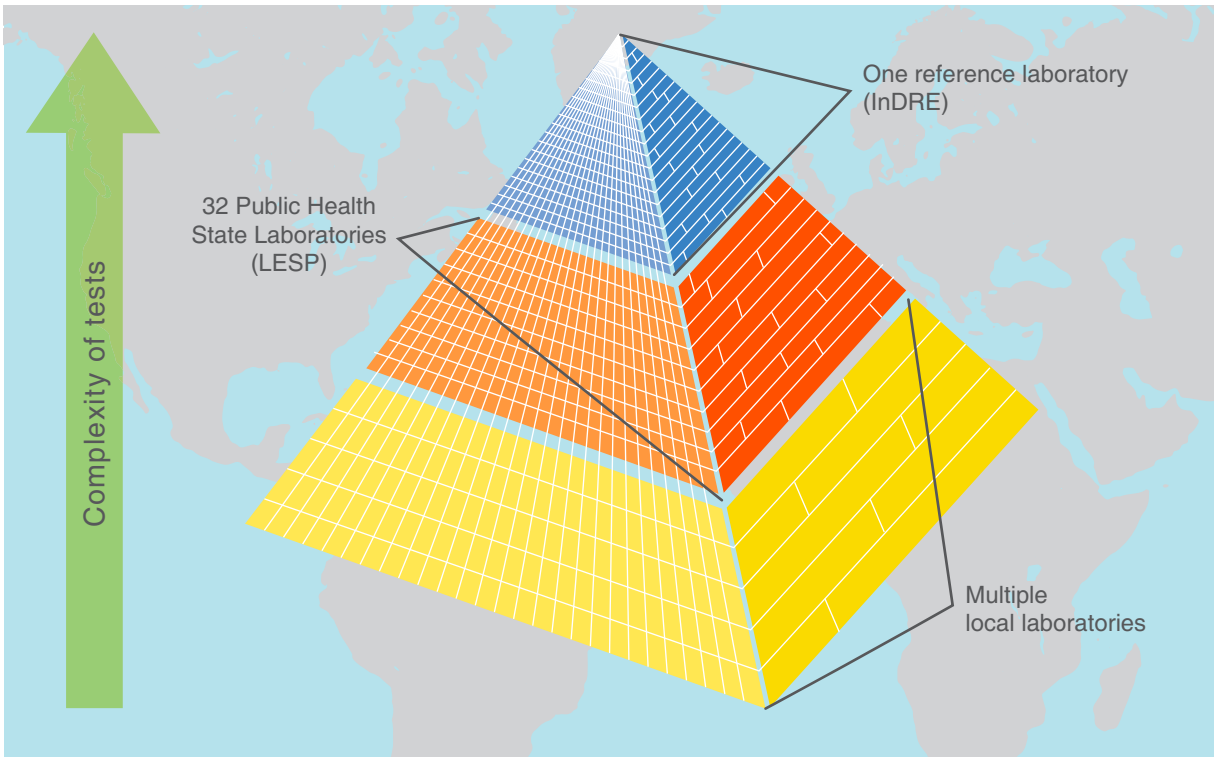

Figure 1. *National Network of Public Health Laboratories pyramidal organization. Design: Francisco Meza Gordillo.*

level with the LESPs and the local level. It was made up of almost 900 laboratories organized by diagnosis. By the end of the 20th century, the RNLSP had 19 LESPs and four were under construction.[12] Each group of laboratories that made the same mandatory diagnosis formed a specific network: the malaria network, tuberculosis network, etc. (Table 2).

The integration process followed by the RNLSP is interesting. From 1947 to 1984, cytology diagnosis was performed in medical units in an assistance model.[13] In the 1970s, the diagnosis of rabies was started in the Regional Laboratory of Virology, which later became the State Laboratory of Public Health in the State of Mexico (Nidia Aréchiga, personal communication). The laboratories for the malaria and tuberculosis programs worked separately. All joined the RNLSP in the 1980s (Table 2).

In the ensuing years, the malaria program received timely information from approximately 250 state and local microscopists (Sonia Galindo, personal communication)

Table 2. National Network of Public Health Laboratories in 1992

Main function	Central laboratory	State laboratories (n)	Local laboratories (n)	Participating states (n)
	Coordination and reference	Diagnosis and liaison	Diagnosis and screening	
Diagnosis				
Malaria	InDRE	3	138	27
Tuberculosis and leprosy	InDRE	10	474	32
Cervical cancer	InDRE	2	40	16
Rabies	InDRE	10	6	13
HIV/AIDS	InDRE	6 LESP 17 CETS	86	32
Cholera	InDRE	16	73	31
Histocompatibility for transplants	InDRE	1	23	9

LESP (*Laboratorio Estatal de Salud Pública*) = Public Health State Laboratory, CETS (*Centro Estatal de la Transfusión Sanguínea*) = State Center of Blood Transfusion, InDRE (*Instituto de Diagnóstico y Referencia Epidemiológicos*) = National Institute of Epidemiological Diagnosis and Reference.
Source: Valdespino-Gómez JL. *Informe técnico. Instituto Nacional de Diagnóstico y Referencia Epidemiológicos Dr. Manuel Martínez Báez, 1992-1993.*

and from the entomology network, which also reinforced the surveillance of other vector-borne diseases. The tuberculosis program was supported by 31 LESPs and more than 700 local laboratories (Susana Balandrano, personal communication).

Another mechanism was the creation of networks in response to some conditions: the National HIV Network in 1986, the National Cholera Network in 1991[14] and the Acute Respiratory Bacterial Infections Network in 2002 (Luis Ángel Sapian López and Isabel Moreno-Camilli, personal communication) (Table 2).

The networks were constantly evolving. Two examples: the diagnosis of exanthematic febrile disease included measles, rubella and dengue; the relevance of the latter motivated the creation of a specific network for dengue, which was expanded towards other arboviroses existing in Mexico or at risk of being introduced. Since 2009, the Network of Influenza and other Respiratory Viruses employed molecular methodologies at the LESPs and five laboratories that support epidemiological surveillance, which belong to different health institutions: Mexican Institute of Social Security, Institute of Social Security and Services for State Workers, General Hospital, National Institute of Medical Sciences and Nutrition and National Institute of Respiratory Diseases (Table 3).

The close monitoring of the performance of each LESP and the implementation of quality and biosafety management systems since 2002 (Celia González Bonilla and Lucía Hernández, personal communication) provided a framework of opportunity and reliability to the development of the RNLSP.[15]

In order to harmonize laboratory work with epidemiology, 27 priority diagnostic algorithms were defined, organized in 18 diagnostic networks, where all LESPs had to participate (Tere Martín Escobar, personal communication) (Table 3).

In the 1990s, at InDRE there was intense production of reagents and supplies that ensured diagnosis in the LESPs. Methodologies were introduced for large-scale seroepidemiological studies (Herlinda García Lozano, personal communication), in addition to molecular techniques to identify and characterize agents,[16] as well as evaluation of the applicability of available commercial tests in the Mexican population (Roberto Vázquez Campuzano personal communication), which supported the anticipatory nature of surveillance.[17]

The InDRE implemented more than 300 algorithms of its own, including those for polio, mycosis, cysticercosis, free-living amoebas and pathogens involved in bioterrorism, as well as procedures to determine resistance to antiviral and antibacterial drugs and for the production of biological reagents.

Flow of samples and information. Chain of custody and biosafety

The pulse and capillarity of the pyramidal organization, unnoticed by the external user, are the result of the efforts of thousands of workers who mobilize clinical-epidemiological information with samples (human tissue and fluid, the pathogen itself, entomological specimen or genetic material), which are considered of high epidemiological value. Each sample is taken, identified, preserved, packed, transported from any location to its place of processing and final safekeeping (or disposal) in a network laboratory. This dynamic process has two elements: the care of the sample with its associated information (chain of custody) and the protection of professionals, population and environment (biosafety).

The biological materials protected in sample banks, some preserved since eight decades ago, are an invaluable heritage for research and reference.

Table 3. **National Network of Public Health Laboratories**

Diagnostic algorithm*		Conditions†	Start of the network in Mexico	Start of diagnosis at ISET-InDRE
1	Cervical cytology	Cervical cancer	1947‡	1985
2	Malaria	Malaria by *Plasmodium vivax* (autochthonous), *falciparum, malariae* and *ovale* (imported), acute Chagas disease, cutaneous leishmaniasis	1955‡	1984
3	Tuberculosis	Pulmonary, extrapulmonary and drug-resistant tuberculosis	1971‡	1987
6	Rabies	Human rabies and in domestic and wild animals	1972	1979
4	HIV/AIDS**	HIV/AIDS infection	1986	1985
5	Entomology	Diseases transmitted by vector mosquitoes, hematophagous bedbugs, poisonous arthropods, ectoparasites and other taxa	1987	1939
7	Acute bacterial diarrheal disease	Cholera, outbreaks of *Vibrio parahemolyticus* and *Escherichia coli* gastroenteritis, *salmonellosis, shigellosis*	1991	1939
8	Brucellosis	Human brucellosis	1992	1939
9	Febrile exanthematous illness	Measles, rubella, congenital rubella, differential diagnosis for mumps, chicken pox, infections by Epstein-Barr virus, parvovirus B19 and other exanthematous viruses	1992	1972
10	Chagas disease	Acute, congenital or chronic Chagas disease	1994	1939
11	Leishmaniasis	Cutaneous, mucocutaneous, diffuse cutaneous and visceral leishmaniasis	1994	1939
12	Whooping cough	Whooping cough and pertussis-like syndrome	1995	1942
13	Dengue and other arboviroses††	Dengue, Zika, Chikungunya, West Nile virus disease, yellow fever	1995	1978
14	Rotavirus and other enteroviruses	Gastroenteritis caused by rotavirus, norovirus, sapovirus, astrovirus, enteric adenoviruses 40 and 41	1996	1994
15	Influenza and other respiratory viruses	Influenza and infections caused by respiratory syncytial virus, human metapneumovirus, parainfluenza 1, 2, 3 and 4 viruses; coronavirus 229E, OC43, HKU1, NL63, adenovirus, rhinovirus, enterovirus and bocavirus	1997	1951
16	Leptospira	Human leptospirosis	1997	1993
17	Hepatitis	Hepatitis A, B, C	1998	1973
18	Acute bacterial respiratory infections	Severe acute respiratory infections and invasive infections caused by *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae*	2002	1980
19	Rickettsiosis	Spotted Rocky Mountain Fever, epidemic typhus, murine or endemic typhus	2016	1973
20	Sexually transmitted infections‡‡	Syphilis, genital herpes, lymphogranuloma venereum, gonococcal urethritis and cervicitis, non-gonococcal urethritis, mucopurulent cervicitis, vaginal discharge, pelvic inflammatory disease, human papillomavirus	2016	1974

*2019 valid names are used. Each diagnostic algorithm constitutes a laboratory network.
†Those indicated in diagnostic algorithms valid in 2019 are mentioned.
‡Laboratories coordinated by preventive and control programs. The Cervical Cancer Quality Control Laboratory started operating until 1985.
**In the 1970s, the reference laboratory of the Eliseo Ramírez Center for sexually transmitted infections was integrated to the ISET. The network started as Network for HIV and other Sexually-Transmitted Diseases.
††Started operating in the Febrile Exanthematous Illness Network.
‡‡Operated from 1985 to 2016 within the Network for HIV and other Sexually-Transmitted Disease.

InDRE response to infectious disease events

Some epidemic events (such as cholera, HIV/AIDS and dengue) motivated the creation of networks. It is important to highlight the special response given to measles and the influenza pandemic.[18-22]

The management of the cholera outbreak in 1991 was emblematic for the training the InDRE professionals cascaded to the LESPs, which reproduced it in 239 local, public and private laboratories.[23] The InDRE carried out the genotyping and antimicrobial susceptibility testing, developed and sent biological reagents to the LESPs, supervised and evaluated screening in the states.[24]

This successful technology transfer model would be used to deal with outbreaks and health emergencies by dengue, cholera and leptospirosis in hydrometeorological events, even to support Central American countries.

In 2001, anthrax diagnosis was established as a preparation for potential bioterrorism actions; evidence of low risk for the Mexican population was provided (Hiram Olivera Díaz, personal communication). Biological risk management was strengthened in the RNLSP.

Influenza A (H1N1)pdm arrived to Mexico when the classical methods of virology and molecular biology were sufficiently developed to carry out confirmation, subtyping, isolation, sequencing, bioinformatics analysis and antiviral resistance surveillance (Ernesto Ramírez González and Irma López, personal communication). InDRE deployed a rapid response –initially 24 hours a day, every day of the week– and transferred molecular techniques in real time that expedited the response and population impact assessment. The special response to the pandemic (Command System for Incidents) included the entire RNLSP.[25,26]

Bioterrorism, early alert and containment

Since 1999, InDRE officially participates in the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological and Toxin Weapons and on their Destruction (Irma Hernández-Monroy, personal communication).

In 2001, in addition to the diagnosis of West Nile virus, SARS Co-V and anthrax, the diagnostic capacity for *Francisella tularensis*, *Yersinia pestis,* variola virus and botulinum toxin was added to the Institute,[27-29] in view of the risk of deliberate release.[30]

That same year, Mexico joined the Global Health and Safety Initiative. In the network of laboratories of this initiative, InDRE participates in the G7+Mexico, which allowed to maintain the capability to address threats to national health security.

In 2010, InDRE's effort was recognized in the United States, and it was included in the Laboratory Response Network (LRN), a select network of laboratories where the Centers for Disease Control and Prevention (CDC)), the Department of Health and Human Services (DHHS), the US Department of Agriculture (USDA), the Food and Drug Administration (FDA), the Federal Bureau of Investigation (FBI) and other USA agencies do participate.

Only Canada, Australia, the United Kingdom and Mexico are LRN member countries and maintain standard laboratory procedures to respond to bioterrorism events, emerging infectious diseases, chemical terrorism and other public health contingencies.

Bank of reference biological material

Biological materials under institutional protection (strains, human samples, entomological material, genetic sequences) and others acquired from international banks (standards, controls) are essential to achieve high quality in the performance of a reference laboratory.

An example is the Collection of Arthropods of Medical Importance, started in 1938 and cataloged since 1987. The continuous incorporation of specimens has enabled having the largest collection in Latin America (Sergio Ibáñez, personal communication).

The registration, classification and packaging of the biological material to be brought to the new InDRE headquarters was carried out under strict conditions of biosafety and biocustody, in compliance with national and international regulations.

The construction of the new InDRE facilities

In 2007, given the obsolescence and insecurity of the facilities for workers and its immediate surroundings, the health authorities recognized the need for a new and modern infrastructure for the InDRE. The document *Bases for the design of InDRE new facilities*, of 2008, noted the conditions of the facilities built in 1935.

The executive project for the laboratory building was developed by an international, specialized company, with a contemporary design and building materials and systems that would optimize operation and maintenance.[31]

Figure 2. *Construction of the new InDRE facilities at Lomas de Plateros, Mexico City.* **A:** *2010, photograph by Rita Flores León.* **B:** *2011, photograph by Amelia Patiño González.*

Table 4. Directors of the Institute of Epidemiological Diagnosis and Reference, 1990-2019

Director	Period
José Luis Valdespino Gómez	1990-1994
Ana Flisser Steinbruch	1995-2000
Elsa Josefina Sarti Gutiérrez	2001-2003
Ignacio Federico Villaseñor Ruiz	2003-2007
Celia Mercedes Alpuche Aranda	2007-2012
José Alberto Díaz Quiñonez	2012-2019

The administrative building was designed in the tradition of the Mexican architectural school (Fig. 2). Total constructed area, almost 17,000 m^2 of laboratories would boost the fulfillment of the InDRE mission in the national and international spheres (Smith Carter-ICEMEX, InDRE. *Diseño esquemático/bases de diseño*, 2008).

Discussion

In 1989, ISET became the InDRE and dedicated its activity to epidemiological surveillance and referral. The name change of the institution, from ISET to InDRE was a gradual, discreet process, without ceremony, during the first quarter of that year (Alejandro Escobar, personal communication).

In 1985, the ISET had already been appointed head of the National Network of Public Health Laboratories, which obtained legal support in 1997 and 2010. These decisions helped to address the HIV/AIDS, cholera, dengue, measles and influenza epidemic events, which required a special response from the RNLSP.

By the end of this crucial institutional period, with the RNLSP in operation but with new epidemiological challenges such as the influenza pandemic, it became clear that the InDRE infrastructure was inappropriate. The 1935 art deco building was replaced by state-of-the-art architectural installations, to consolidate the intense national work and boost global participation. The list of directors for the 1990-2019 period is presented in Table 4.

InDRE and its diagnostic networks constitute a milestone for Latin American public health of the 21st century.

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SPECIAL ARTICLE

From the handling of an outbreak by an unknown pathogen in Wuhan to the preparedness and response in the face of the emergence of Covid-19 in Mexico

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Abstract

On December 31, 2019, the Chinese health authorities informed the international community, through the mechanisms established by the World Health Organization (WHO), of a pneumonia epidemic of unknown etiology in Wuhan, Hubei Province. The first cases were reported early in that month and were linked to a history of having visited a market where food and live animals are sold. On January 7, 2020, isolation and identification of the culprit pathogen was achieved using next-generation sequencing, while the number of affected subjects continued to rise. The publication of full-genomes of the newly identified coronavirus (initially called 2019-nCoV, now called SARS-CoV2) in public and private databases, of standardized diagnostic protocols and of the clinical-epidemiological information generated will allow addressing the Public Health Emergency of International Concern (PHEIC), declared on January 30 by the WHO. With this document, we intend to contribute to the characterization of the pneumonia epidemic, now designated coronavirus disease (Covid-19) review the strengths Mexico has in the global health concert and invite health professionals to join the preparedness and response activities in the face of this emergency.

KEY WORDS: *New coronavirus. SARS-CoV2. Covid-19. Mexico.*

De la atención de un brote por un patógeno desconocido en Wuhan hasta la preparación y respuesta ante la posible emergencia del 2019-nCoV en México

Resumen

El 31 de diciembre de 2019, las autoridades chinas de salud informaron a la comunidad internacional, a través de los mecanismos establecidos por la Organización Mundial de la Salud (OMS), de una epidemia de neumonía con etiología desconocida en Wuhan, provincia de Hubei. Los primeros casos se notificaron a inicios de ese mes y se vincularon al antecedente de visitar un mercado de comida y animales vivos. El 7 de enero de 2020 se logró el aislamiento y reconocimiento del patógeno responsable mediante secuenciación de siguiente generación, mientras el número de afectados continuaba en ascenso. La publicación de genomas completos del nuevo coronavirus identificado (inicialmente denominado 2019-nCoV, ahora designado SARS-CoV2) en bases de datos públicas y privadas, de protocolos diagnósticos estandarizados y de la información clínica epidemiológica generada permitirá atender la Emergencia de Salud Pública de Importancia Internacional (ESPII) declarada el 30 de enero por la OMS. Con este documento pretendemos aportar a la caracterización de la epidemia de neumonía, ahora llamada enfermedad por coronavirus (Covid-19), revisar las fortalezas que tiene México en el concierto de la salud global e invitar a los profesionales de la salud a incorporarse a las actividades de preparación y respuesta ante esta emergencia.

PALABRAS CLAVE: *Nuevo coronavirus. SARS-CoV2. Covid-19. México.*

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Characterization of the pneumonia epidemic of unknown etiology

Coronaviruses belong to the *Coronaviridae* family and are divided in four genera: alpha, beta, gamma and delta. The former two have the ability to infect mammals, while gamma and delta mainly infect birds, with some potential to infect mammals.[1]

Alpha and beta coronaviruses usually trigger respiratory symptoms in humans and gastrointestinal manifestations in other mammals. Almost all coronaviruses that have affected humans appear to come from bats.[1,2]

Coronavirus particles measure around 160 nm and their genetic material is contained in a 27- to 32-kb ribonucleic acid strand. The 5' terminus encodes 16 non-structural proteins related to transcription and replication processes, while the 3' terminus encodes membrane, spike, nucleocapsid and envelope structural proteins.[1]

Viral pathogenicity depends, to a large extent, on the type of receptor and the organs where the virus is expressed. Regarding the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV) and SARS-CoV2, the receptor is angiotensin converting enzyme 2 and other proteases that are widely distributed in lung tissues.[3-5]

The report of the first cases of this epidemic can be traced to December 8, 2019. From the clinical molecular analysis of samples obtained from lung tissue, nasopharyngeal smear and blood from 42 patients who had respiratory symptoms and shared a history of having visited an animal market, 15 positive results were obtained identifying a coronavirus that had not been previously observed, so far named 2019-nCoV.[2,6]

Early recognition of the pathogen as a coronavirus with similarities to SARS-CoV (microscopic characteristics, previous history of contact with animals, respiratory symptoms), the causative agent of severe acute respiratory syndrome (SARS), facilitated the definition of the surveillance system (the same that was used during the 2003 outbreak, responsible for more than 8000 cases in 26 countries).[6,7]

The operational definition that was used at the beginning of the outbreak in Wuhan was based on the proposals for surveillance and the report of the 2003 and 2012 outbreaks and included the presence of four criteria: fever (quantified or not), radiological evidence of pulmonary involvement, low leukocyte or lymphocyte count and no improvement after three days of antibiotic treatment, or presence of the first three and a history of contact in the Wuhan market.[8-10]

On December 31, health authorities in China reported on the outbreak to the international community through the WHO, making public the preliminary epidemiological clinical information.[8,11,12]

On January 1, 2020, Chinese health authorities closed the market associated with the outbreak to study and identify the source of contagion, which continued to be unknown.[6]

On January 7, while the number of those affected continued on the rise, health authorities in China managed to identify the pathogen, an information that was released days after the first death, reported on January 9, 2020. On January 12, the genomic sequence of the new pathogen was shared, followed by others deposited on the Genbank platforms and on GISAID (Global Initiative on Sharing All Influenza Data). It was the beginning for the use of standardized virus detection protocols and thereby, of the response from different sectors.[13-16]

On January 13 and 15, the first imported cases were reported in Thailand and Japan, respectively; gradually, the outbreak reached other territories.[17] Chinese authorities decided to place infrared thermometers in airports and bus and railway stations.

Since January 21, the WHO started publishing reports on the situation in affected countries. Among the actions of response by health authorities in affected countries, active search for cases and close follow-up of contacts was requested by WHO.[18] On that same date, a risk analysis of viral dispersion was published, and places where the virus was more likely to spread to were alerted, with these calculations being replicated later with different methodologies.[19-22]

On January 23, phylodynamic analyses from 23 sequences were reported to show no evidence of an intermediate reservoir between the source of infection and humans. Mathematical estimates calculated the size of the outbreak to be approximately 4000 cases, a figure that suggested that the transmission chains were maintained by cases with not too severe symptoms that not seeking medical help.[23,24]

On January 26, evidence of transmission among humans was strengthened with one of the cases in Vietnam.

On January 30, the WHO announced the situation as a new Public Health Emergency of International Concern (PHEIC). In the report, special emphasis was made on strengthening technical and material supply capacities in laboratories and health infrastructure.[13,18,25] A PHEIC is an event that represents the risk of international

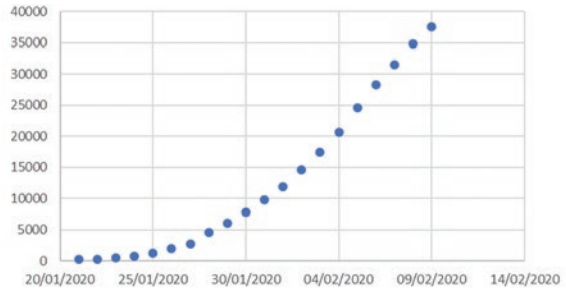

Figure 1. *Accumulated cases of Covid-19 since the World Health Organization started issuing daily reports.*

spread of a disease, which requires a coordinated response; the definition assumes that the situation is serious, sudden, unusual and unexpected.[26,27]

As it has occurred with other PHEICs, the operational definition has been dynamic. On January 18, a history of having visited Wuhan (regardless of having visited the market, which was closed on January 1) or contact with Wuhan patients who had had respiratory symptoms within the previous 14 days was included. For the confirmation of cases, using some molecular technique is necessary:[8,14]

- Polymerase chain reaction aimed at identifying the 1a or 1b reading frame that codes for viral nucleocapsid protein.
- Isolation of viruses.
- Findings of viral genetic information that relates the case to other sequences.

In the January 31 report, the number of confirmed cases had exceeded the figures reported for the outbreak of SARS in 2003 (Fig. 1). Of the 106 confirmed cases outside China, seven were reported to be asymptomatic. As of February 1, 2020, the operational definition for the outbreak defines as suspicious any patient with severe acute respiratory infection with a history of fever and cough that requires in-hospital care and whose etiology cannot be explained, in addition to the following:[28]

- Having traveled to or lived in Wuhan within 14 days prior to the onset of symptoms.
- Being a health worker whose activities are carried out in centers where people with respiratory diseases are treated, regardless of his/her history of travels or residence.

That day, France was reported to have diagnosed the first health worker outside China, in addition to information from Germany and Japan being compiled supporting the existence of transmission among humans. By February 5, Belgium joined the list of countries with confirmed cases. The WHO designated the disease as Covid-19 (acronym for Coronavirus disease-2019) and launched a USD $ 675-million preparedness and response plan as a mechanism to prepare countries lacking the necessary infrastructure to face the emergency.[29]

On February 6, 72 WHO member states were reported to have implemented travel restrictions. Of note, only 32 % of them officially notified the WHO.[30]

By February 8, with 24 affected countries, the WHO response included collaboration with various stakeholders of society, from specific sectors such as financial, agricultural, touristic and academic entities to the general public, a task in which the role of social networks has been central.[31,32]

On February 9, in its daily report, the WHO announced that projects aimed at updating health personnel protection measures, a field data collection tool and translation of available materials on the outbreak into several languages were underway.[33]

Epidemiological estimators for Covid-19 have varied as new information has become available; however, the basic reproduction index calculations remain positive, with incubation periods ranging from two to 14 days. Male adults remain with the highest proportion among diagnosed cases (71 %); elderly individuals with comorbidities represent the population group that is most susceptible to die from the infection, with median age at diagnosis being around 45 years.[8,34-37]

Preparedness and response in Mexico

The Ministry of Health of Mexico has made publicly available dissemination materials with general information on the situation of the Covid-19 outbreak since its inception. On January 30, it issued a preventive notice about travelling to the Hubei Province in China, and every day it publishes a report with verified data from official sources.[38]

In addition, the National Epidemiological Surveillance System developed the *Standardized guidelines for epidemiological and laboratory surveillance of 2019-nCoV-related disease*, a document that establishes operational definitions, handling of samples, prevention measures and risk control, in addition to providing a diagnostic algorithm in the face of the risk of arrival of the emerging pathogen.[39] This document considers different areas of epidemiological surveillance in the event of an international emergency, and as an appendix it presents a special form for the study of cases, follow-up of contacts, recommendations for international points of entry and a line of action for health workers who handle a suspicious case.

The importance to continue with the updates of this guideline –the first one was on February 7, 2020– lies in ensuring the rapid detection of imported cases and thus avoiding the generation of secondary transmission chains.[39]

In Mexico, a person of any age who has an acute respiratory illness and who has a history of travel to or stay in the Hubei Province, China, or who has been in contact with a confirmed case or an individual under investigation for up to 14 days prior to the onset of symptoms is considered a Covid-19 suspicious case. Confirmation is established with standardized methods by the "Dr. Manuel Martínez Báez" Epidemiological Diagnostic and Reference Institute (InDRE – *Instituto de Diagnóstico y Referencia Epidemiológicos*).

The investigation of suspect cases must be carried out in accordance with the standard protection measures and based on the mechanism of transmission (by droplet and contact).

- *Standard precautions:* handwashing (soap and water) or hand hygiene (alcohol gel at concentrations higher than 70 % at the five moments defined by the WHO), use of gloves, use of facemask with facial protection and waterproof gown if there is the risk of splashing to the eyes and face, disposal of contaminated clothing in a red bag, use of rigid containers for sharps and never re-cover the needles once used.
- *Precautions for transmission by droplets:* keep a distance of one meter with the patient, keep the door closed during patient care, monitor visitors, personalized use of medical equipment such as stethoscope, thermometers or blood pressure cuffs; if this is not possible, clean and disinfect between each patient with 70 % ethyl alcohol; assignment of a single room for the suspected case or isolation of the cohort, transfer of the patient only for special situations and notification to the care team about these measures.
- *Precautions for aerosol transmission:* use of N95 facemask in procedures that generate aerosols such as aspirations, intubations, bronchoscopies and cardiopulmonary resuscitation.

Working lines were established for health personnel in contact with suspicious cases, with differences for the levels of care existing in Mexico.

Upon identification of a case that meets the travel history or risk contact, the first measure for the primary care physician will be to provide a surgical mask to the patient. From that moment on, the doctor will assess the patient in an isolated space with protective measures such as disposable gown, glasses and gloves, and will decide if the case meets the operational definition; if the case is positive, the doctor will use a N95 mask for protection and will take samples and notify the corresponding epidemiological instance. Should hospitalization be necessary, the patient should be sent to the appropriate level, monitored by the epidemiology area .

At secondary and tertiary care it is assumed that patients will arrive with data consistent with respiratory distress, in which case the workflow would be similar to that of primary care. At these levels, isolated beds for patients will be necessary, as well as the use of specialized protective equipment for health personnel, such as facemask, disposable gown and protective goggles, the latter because there is evidence of potential transmission by that route.[40] The epidemiology team is established as a link to provide information on the follow-up of each case.

The samples for Covid-19 diagnosis are nasopharyngeal and pharyngeal exudate taken with dacron or rayon swabs, with the tubes being transported together (in viral medium at 4 °C) to increase viral load. If the patient is intubated, bronchoalveolar lavage fluid should be obtained (at least 1 mL of aspirate and 1 mL of transport medium is required) and, in case of death, lung biopsy (2 cm^3). The samples must be obtained during the first five days of clinical presentation and be transported in a triple packaging system, in accordance with established guidelines.[39] If the case is confirmed, patient isolation is recommended for up to 14 days after the resolution of clinical manifestations. The confirmation algorithm considers differential diagnosis with other respiratory pathogens such as influenza, parainfluenza, adenovirus, respiratory syncytial virus, Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV and other coronaviruses.[41]

Current situation with Covid-19 is of an uncertain outlook. Ignorance on the source of dispersion, in addition to not having a specific treatment or preventive vaccine, puts us in a challenging scenario where collaboration, information exchange and transparency between different sectors of society are valuable means of protection.[42,43]

During 2019, a total of 60 municipalities in Mexico (with 32,851,129 inhabitants) received 15,072,653 visitors by air from countries that have Covid-19 confirmed cases so far (Fig. 2). This puts into perspective the connectivity of the different regions of the country,

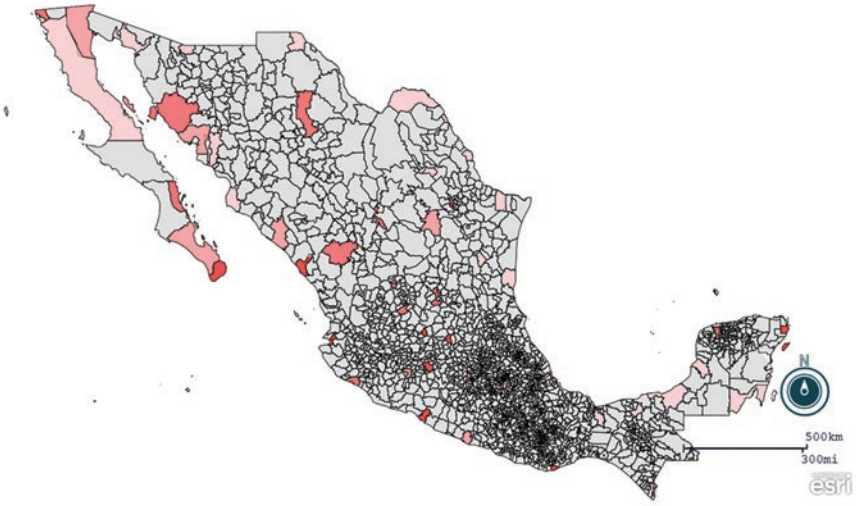

Figure 2. *Choropleth map representing the number of visitors from countries with Covid-19 confirmed cases, by municipality, until November 2019. Data from the Ministry of Foreign Affairs.*

mostly densely populated territories. These destinations would represent the areas of highest risk for arrival of the pathogen.

Considerations for health workers

Previous epidemics have left useful lessons to mankind. At this moment of the Covid-19 outbreak, effective dissemination of information is key for transmission chains to be cut. The WHO has dedicated a public site to the dissemination of courses for continuous learning that contains updating modules, at the level of response in both public and clinical and laboratory health.[44-47]

In a coordinated way, the academy and private institutions have created scientific discussion forums, visualization platforms and dissemination of information on the outbreak that allow real-time traceability of events. Although they will not always coincide with official figures, these tools represent a modality for the study of the outbreak that the public health sector had not used ever before.[14,46,48,49]

Conclusions

The close dynamics we have with other species has caused the emergence of epidemics related to unknown pathogens or that we considered under control. In terms of global health, it is difficult to define nationalities or territories. The Covid-19 outbreak will leave lessons on the power of collaboration before a PHEIC, regardless of how many countries it affects. In Mexico we must learn from the lessons and strategies of the countries that have been affected. New knowledge is generated every day that, if used properly, will allow us to face the introduction of this and other emerging diseases.

Conflict of interests

None

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REVIEW ARTICLE

Research and research ethics committees and the obligation for them to operate in accordance with the principle of the social covenant

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Abstract

The relationship between the social covenant, ethics and scientific research is highly important for society. Economic prosperity and better health are two of the main reasons why society supports science, without society itself being able to determine the nature of the research that is to be implemented; this is decided by Research Committees (RCs) and Research Ethics Committees (RECs). This article analyzes how the work of RCs and RECs must have a social covenant and represent the interests of society in order to promote its trust in research.

KEY WORDS: *Research Committees. Ethics Committees. Social covenant. Ethics. Mexico.*

Los comités de investigación y ética en investigación y la obligación de que operen de acuerdo con el principio de la alianza social

Resumen

La relación entre alianza social, ética e investigación científica es extremadamente importante para la sociedad. La prosperidad económica y la mejor salud son dos de las principales razones por las cuales la sociedad apoya a la ciencia, sin que la sociedad misma pueda determinar la naturaleza de las investigaciones que serán implementadas; esto último lo deciden los comités de investigación (CI) y los comités de ética en investigación (CEI). En este artículo se analiza cómo el trabajo de los CI y CEI debe tener una alianza social y representar los intereses de la sociedad para promover la confianza de esta en la investigación.

PALABRAS CLAVE: *Comités de investigación. Comités de ética. Alianza social. Ética. México.*

Introducton

The implicit existence of the social covenant is precisely the reason why the ancient Greeks called ethics "the political science" (*episteme politike*), that is, the science of the city or the science to be a good citizen.[1] In modern world society, science, as a systematic process of rationality, increases its importance when it involves research, because it brings about practical benefits for society in general. In turn, society, through public policy decisions, assigns economic resources to research in order to accelerate scientific progress, without being able to determine the nature of the research that will be implemented; the latter is decided by research committees (RCs) together with research ethics committees (RECs). To the extent that the work of RCs and RECs is an activity carried out by humans, the decisions of the

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committees will reflect the emotions, values and beliefs of their members, which affects the way science is perceived and implemented and how investigations are loyal to the social covenant.

The social covenant, a science-inherent principle

The word covenant derives from *convenire,* Latin word that means to come together, to agree. The dictionary of the Royal Spanish Academy defines the Spanish word for covenant, *alianza*, as the "action of forming alliances".[2] Researchers and members of the RCs and RECs must regard loyalty as the obligation that gives meaning to the social covenant. Therefore, they have fiduciary responsibilities. The responsible fulfillment of the fundamental commitments (where loyalty emanates from) by researchers and RCs and RECs strengthens society's confidence in scientific research. When one of the parties' own interest threatens or violates the legitimate benefits of the other, the primary objective of scientific research is impinged: the generation of valid information, with or without immediate practical ramifications, to the benefit of society.[3,4]

Currently, by law, only research proposals approved by RCs and RECs can be implemented in Mexico. Decision-making by RC and REC members in the assessment of research projects comprises more than theoretical obligations expressed in the law, in regulations and in ethical principles, it involves the character traits of the RC and REC members as well.[5] Hence, it is not surprising that the work of RCs and RECs can sometimes be controversial, especially when they reject research protocols with innovative ideas and with the possibility of generating results that would improve the country's health system, because RC and REC members do not understand the methods whereby the investigations will be carried out. This rupture between the social covenant and the RCs and RECs also occurs when they cease to function as a critical body with clear social responsibility and bias their judgments in deference to a researcher or group of researchers who are perceived with authority or reputation.

When RCs and RECs evade their responsibility with the social covenant in the evaluation of research protocols, they abandon the probability of promoting improvements in health, wellbeing or knowledge of the population. The following is a real and current example where the social covenant is dodged:

– Multicenter research protocol of descriptive, exploratory, retrospective cross-sectional design, which raises an original and relevant research question for the improvement of the quality of life of adolescent women with intellectual disability. As part of the data collection techniques, the methodology refers to the review of medical records with the sole purpose of generating information regarding menstrual hygiene of this group of women. The protocol properly specifies how the anonymity and confidentiality of personal data will be maintained. In their written ruling, the RC and the REC of the hospital considered that the research proposal was scientifically relevant, that it was methodologically well designed and that it met the ethical requirements; however, they rejected the protocol, arguing that hysterectomies had never been practiced in women with intellectual disability in the hospital.

Considering the assertion by the RC and REC that no hysterectomy was found in women with intellectual disability, we might ask ourselves, how did they guarantee the scientific rigor and validity of the results of their search? Is it justified that the RC and REC members implemented the research by their own initiative without prior authorization from the authors of the protocol? How did they maintain scientific and ethical rigor without having followed the protocol they ultimately did not approve?

By offering their services, RCs and RECs are accepting a fiduciary responsibility and the responsibility to act in accordance with nationally and internationally established criteria. Their action becomes idiosyncratic when it does not proceed in agreement with these responsibilities, which, consequently, prevents the accomplishment of the benefits that the social covenant entails for society.

Authorship and its relationship with the social covenant

An author is considered as a collaborator who has made substantive intellectual contributions to the protocol of an investigation, and then to the article where the results will be published. Anyone who appears as an author must assume responsibility for the following three conditions:[6]

1. Making important contributions to the design or data collection or analysis.
2. Performing a critical and substantial review of intellectual content.
3. Approving the finished work.

The names of collaborators who do not meet the three authorship criteria should appear in the Acknowledgments section.[6]

Authorship entails important implications and, consequently, academic, social and economic pressures that exacerbate deeply established anxieties in individuals and that, when interacting with each person's nature, define an area of possible behaviors. In hospital units, directors or heads of clinical research and researchers are simultaneously required to maximize scientific productivity. This powerful pressure is what, in many cases, defines scientific research practice morals (from Latin *moralis*, that which is customary[2]). The following is real case that illustrates a common and generalized practice:

– A multicenter sectoral investigation must have the approval of the RCs and RECs of each participating center. A prerequisite demanded by directors or heads of clinical research (in order for the project to be able to be submitted for evaluation by the RCs and RECs of the corresponding hospitals) is that the protocol has to mention a doctor or health professional serving at the potentially participating hospital as a "responsible researcher", with the instruction that this "responsible researcher" should appear as an author. This requirement is established in the forms (of each invited hospital) the researcher must complete to submit the protocol for evaluation by the committees. Although this is the prevailing morals, i.e., that which is customary, an ethical infraction occurs due to the fact that these "responsible researchers" of participating hospitals, which will appear in the list of authors, sometimes only favor or allow access to information or databases or medical records, which are activities that do not justify assuming the role of an author in an investigation. However, failure to comply with this prerequisite makes for a protocol to be rejected since the beginning under the argument that "their hospitals are not only providers of data or samples".

Unjustified authorship gives rise to a series of ethical deliberations: on one hand, it is always a lie and, therefore, an ethical infraction, since an individual obtains credit for something he has not done and can use to obtain a personal benefit. On the other hand, it is a testimony of the nature or way of thinking and being of the agents involved, in the light of the expectations, values and interests that motivate them, and in the way this influences their judgments and decisions.[5] Furthermore, it represents a strong longing for increasing productivity (to publish at all costs), which undermines the scientific foundation on which research should be based: the responsible search for the truth. By rejecting a protocol whose legitimate authors refuse to obey the mandate of assigning a spurious authorship, RCs and RECs cease to promote the generation of scientific knowledge they are bound to by the social covenant.

RCs and RECs professional loyalty

In Mexico, the groups that independently assess research protocols are three: RCs, RECs and biosafety committees.[7,8] We have focused this article on the former two because they generally assess the largest number of protocols and for having overlapping functions. Briefly: for a REC to determine that a research proposal is ethical, it must evaluate its social and scientific importance, its validity and methodological plausibility, the appropriateness of the selection criteria, the risk/benefit ratio and the informed consent documents,[4,9] which are criteria that also have to be examined by the RC.[7] The reason why there must be two groups with overlapping activities is not defined. The essence of the work of the RECs should not be restricted to the informed consent of the research subjects.[4,9] And the methodological aspects assessed by RCs are not alien to ethics either.[4] Research ethics is immersed in research itself; hence, both RCs and RECs duty is to maintain high ethical standards, nationally and internationally defined, in the conduction of an investigation in order for it to meet its purpose: the social covenant.

Prior to being implemented, multicenter studies must be approved by the RCs and RECs of each participating center. The variety of arguments to reject or approve an investigation with modifications indicates how the RCs and RECs of different centers see the same proposal. The differences in justifications depend on the RCs and RECs nature or way of being. To illustrate this, let's go back to the first case, given that it is about a multi-center research proposal:

– In one hospital, the RC and REC rejected the protocol because of "never having performed hysterectomies in women with intellectual disability"; in another, it was objected due to "the possible existence of risky situations for the hospital". Both hospitals are medical care and research reference centers; other hospitals approved the proposal. By denying the research proposal, RCs and RECs violated their professional loyalty (immersed in the social covenant) by conferring

primacy to the interests of the hospitals they belong to, instead of considering the interests of the population of women who would benefit from the research outcomes. The best interest of patients may not be that of the hospital, which could be more interested in avoiding legal aspects, or judgments or opinions of the scientific or medical community itself.

In sum, RCs and RECs will contribute little to the improvement of individual and collective health and wellbeing in health services if they do not understand the nature of their work and its relationship with the social covenant. Professional loyalty emerges from the nature (*ethos*) of each member of the RCs and RECs and from the fundamental commitments they individually and as a whole have with society.

Conclusion

Although there are national guidelines for the integration and operation of RECs and RCs, current reality of the tasks of the committees underscores the need of changes in order to favor for them to operate in accordance with the social covenant and scientific research ethics.

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REVIEW ARTICLE

The colors of adipose tissue

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Abstract

Adipose tissue is an endocrine organ with high metabolic activity. Countless adipose tissue-secreted adipokines and lipokines, as well as peptides and lipids with biological activity have thus far been discovered. Both white and brown and beige adipose tissue are known to contribute to energy homeostasis and metabolic regulation. The purpose of this review is to report on the most recent findings related to adipose tissue according to its color and its relationship with metabolic alterations associated with obesity. After a review of the specialized literature, white, brown and beige adipocyte populations were identified to be able to coexist within the same structure, and to modify global metabolic state in physiological or pathological situations.

KEY WORDS: *Adipose tissue. Adipocyte. Metabolism.*

Los colores del tejido adiposo

Resumen

El tejido adiposo es un órgano endocrino con gran actividad metabólica. A la fecha se han descubierto innumerables adipocinas y lipocinas, péptidos y lípidos con actividad biológica, secretadas por el tejido adiposo. Se sabe que tanto el tejido adiposo blanco como el pardo y el beige contribuyen a la homeostasis energética y a la regulación metabólica. Esta revisión tiene como finalidad comunicar los hallazgos más recientes relativos al tejido adiposo según su color y la relación de este con las alteraciones metabólicas asociadas con la obesidad. Después de la revisión de la literatura especializada, se identificó que en una misma estructura pueden coexistir poblaciones blancas, pardas y beige, que modifican el estado metabólico global en situaciones fisiológicas o patológicas.

PALABRAS CLAVE: *Tejido adiposo. Adipocito. Metabolismo.*

Adipose tissue basic concepts

Adipose tissue accounts for 20 to 28 % of the body mass of healthy individuals, a percentage that varies according to gender and energy status, so that fat mass can account for up to 80 % of body mass in individuals with obesity. The distribution and localization of said fat mass determine its function. Subcutaneous adipose tissue, localized under the skin, represents the highest proportion of adipose tissue.[1] Visceral adipose tissue surrounds the organs, especially the kidney (perirenal adipose tissue), the intestines (mesenteric and omental adipose tissue), the gonads (epididymal and parametrial adipose tissue), the vasculature (perivascular or periadventitial adipose tissue) and the heart (epicardial and pericardial adipose tissue)[2] (Fig. 1).

Adipose tissue belongs to the group of connective tissues that confer cohesion to organs or systems. A clear example of this function is that of mesenteric

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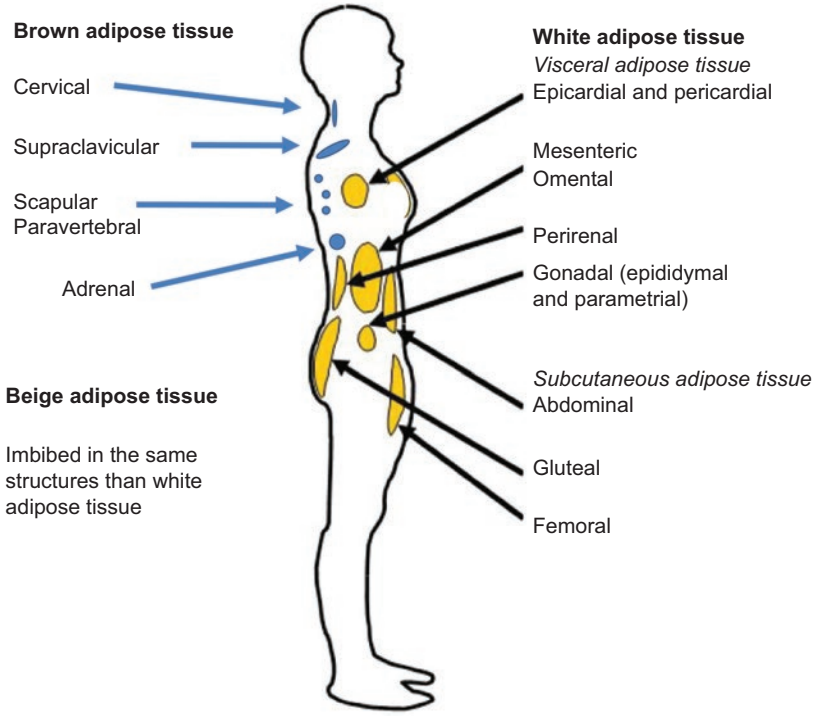

Figure 1. *Localization of white, brown and beige adipose tissue. In yellow, white adipose tissue structures, and in blue, brown adipose tissue deposits.*

adipose tissue, which keeps the convolutions of the small intestine in a more or less constant position.[3] In addition to the function of giving support to structures, adipose tissue very importantly regulates energy balance. Recently, adipose tissue was shown to be not only an energy store or a passive organ of metabolism, but to also influence and participate in energy status. In fact, it has been considered an endocrine organ capable of secreting hormones that travel through the bloodstream to reach their target tissues. Other adipose tissue functions refer to the regulation of physiological processes such as sexual dimorphism, immunity, reproduction, adipogenesis, angiogenesis, extracellular matrix restructuring, steroid metabolism, hemostasis and body temperature maintenance.[4,5]

The performance of these functions is conferred by the variety cell types that make up adipose tissue: adipocytes, preadipocytes, fibroblasts, macrophages, monocytes, vascular stromal cells and innervation cells. The highest proportion of cells in this tissue appears not to be represented by adipocytes, but by the other cells. In fact, up to 80 % of total DNA extracted from adipose tissue comes from vascular cells, fibroblasts, leukocytes and macrophages.[6]

There are three types of adipose tissue according to their functions, coloration, vascularization and structure (Fig. 2):

- White adipose tissue.
- Brown adipose tissue.
- Beige adipose tissue.

White adipose tissue

White adipose tissue is characterized for being a white or yellow tissue with less vascularization and innervation than brown tissue. White adipose tissue fat cells have a size that ranges from 20 to 200 µm and are unilocular, i.e. they contain a single lipid vacuole. In said vacuole, lipids are stored for use when there is energy demand. Of the totality of lipids encompassed by the white adipocyte lipid vacuole, 90 to 99% are triacylglycerols.[3] The triacylglycerols deposited in the lipid vacuole contain enough energy to meet the energy requirements of a healthy adult for at least two months.

White adipose tissue generates a large number of adipokines and lipokines. Adipokines are peptides that act as hormones or messengers that regulate metabolism. Around 40 % of the genes expressed by

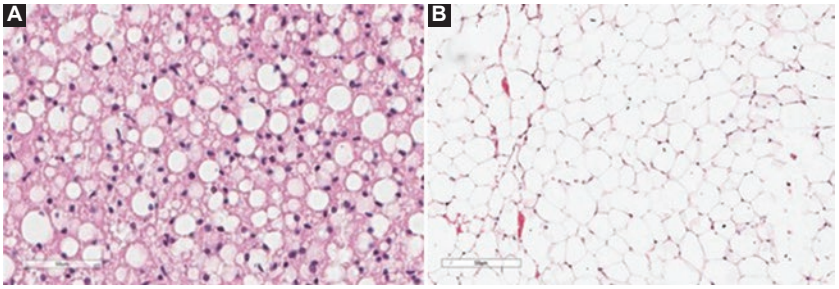

Figure 2. *Brown* **(A)** *and white* **(B)** *adipose tissue histology, staining with hematoxylin and eosin, 40x, 50 µm scale. Notice that brown adipocytes contain several lipid vacuoles, that the tissue is highly innervated and that nuclei are indeterminately located. White adipose tissue is less innervated and contains a large lipid vacuole per cell, which is why the nucleus is located towards the periphery and is observed to be flattened.*

adipose tissue are estimated to be novel in their function, and 20 or 30 % of them are estimated to correspond to secretion proteins.[7] We know that adipose tissue secretes proteins with high versatility of functions related to proinflammatory cytokines, immunity, the complement, the fibrinolytic system, the renin-angiotensin system, lipid metabolism and transport and steroid metabolism enzymes, among others. For these reasons, adipose tissue is considered to be an endocrine organ that produces adipokines such as adiponectin or prokineticin or meteorine-like hormone.[8,9] Lipokines, which are lipid in nature, exert the same function when secreted by the adipocyte and influence on metabolism.

Between the decades of 1950 and 1970, parabiosis studies showed the existence of circulating factors that regulated body weight: when blood from thin rodents was introduced in obese rodents, the weight of the latter was observed to become normalized.[10-12] In 1994, Dr. Friedman and his group first described one of these factors. It was leptin, a protein fundamentally secreted by adipocytes and, therefore, an adipokine. Leptin is made up of 167 aa, it weighs 16 kDa, belongs to the cytokine family and is considered an anorexigenic hormone because it causes satiety. In animals, local infusion of leptin into the hypothalamus reduces energy consumption and body weight.[13] Initially, it was thought that this would be the expected antidote to obesity, but clinical trials showed that the biological effect of the hormone was not significant. In an interview for *The Journal of Clinical Investigation*, Dr. Friedman stated that most patients produce enough leptin; however, its action is decreased in obese individuals, which is regarded as leptin resistance.[14]

Now we know that hyperleptinemia in obesity is associated with leptin resistance, hyperphagia and increased lipid storage capacity and oxidation in adipose tissue and peripheral organs.[15-18]

Subsequently, adiponectin was discovered, which is a 30 kDa adipokine that forms hexamers and dodecamers,[19] and that has high molecular weight associations that promote insulin sensitivity, increase lipid oxidation in muscles and the liver and decrease the expression of adhesion molecules and proinflammatory cytokines. In humans, hypoadiponectinemia is related to obesity, diabetes and metabolic syndrome.[20]

Omentin is also an adipokine with favorable effects on metabolism; it is found at lower concentration in the circulation of individuals with obesity, type 2 diabetes or cardiovascular disease. Omentin exerts its functions by activating insulin signaling pathways and by inhibiting inflammatory pathways and atherogenic processes.[21]

Other adipokines such as resistin, a retinol-binding protein or RBP-4, chemerin and visfatin are increased in the serum of individuals with obesity and promote insulin resistance and cardiovascular risk,[22] thus contributing to metabolic syndrome.

As previously mentioned, there is a group of molecules known as lipokines. De novo lipogenesis in adipose tissue gives rise to fatty acids such as palmitoleate (16:1n7) and fatty acid esters of hydroxy fatty acids (FAHFA), which are attributed favorable metabolic effects.[23] Palmitoleate has been shown to regulate the expression of lipogenic genes in the liver, to promote insulin sensitivity in the liver and muscle tissue,[24] and to antagonize the inflammatory effects produced by palmitic fatty acid in diet-induced obesity animal models.[25-27] Also as a product of de novo lipogenesis in adipose tissue, PAHSA, a FAHFA isomer consisting of a palmitic acid (16:0) and a stearic acid (18:0), is regulated by fasting-postprandial cycles, and

Table 1. Description of some adipokines/lipokines, secreting organ, influence on energy consumption and metabolism

Adipokine/lipokine	Secreting organ or tissue	Orexigenic/ anorexigenic	Metabolic effect
Leptin	Adipocytes, stomach and intestinal epithelium, placenta, muscle, mammary gland and brain	Anorexigenic	Satiety, lipid oxidation, thermogenesis, insulin sensitivity
Adiponectin	Adipocytes	Anorexigenic	Lipid oxidation, hepatic gluconeogenesis suppression, monocyte adhesion inhibition (anti-inflammatory and anti-atherogenic)
Omentin	Visceral adipose tissue vascular stromal cells and intestinal cells	Orexigenic	Increased capture of insulin-stimulated glucose and release of orexigenic peptides in the hypothalamus
Resistin	Adipocytes	Anorexigenic	Resistance to the action of insulin and fatty acid synthesis in liver
Reintol-binding protein-4	Adipocytes	---	Retinol transport and resistance to insulin action due to lower GLUT4 expression
Chemerin	Adipocytes, hepatocytes and lung cells	Orexigenic if chronically infused	Adipogenesis, angiogenesis, pro-inflammatory
Visfatin	Adipocytes in visceral adipose tissue	—	Possible influence on the development of obesity, pro-inflammatory and pro-atherogenic
Palmitoleic acid	Adipocytes	—	Insulin sensitivity, decreased lipogenesis
PAHSA (palmitic acid-hidroxy-stearic acid)	Fasting subcutaneous and perigonadal adipose tissue	—	Insulin sensitivity due to increased glucose capture, increased insulin and glucagon-like peptide-1 secretion, anti-inflammatory

its elevated concentrations have been associated with increased insulin sensitivity.[28] In clinical trials, insulin-resistant patients were shown to have lower PAHSA concentration[29] (Table 1).

The proportion of released adipokines or lipokines with anti-inflammatory action in relation to those of pro-inflammatory and pro-atherogenic action influences on the establishment of the metabolic alterations that accompany obesity. Finally, adipokine production imbalance is a reflection of adipocyte functionality loss under conditions of energy excess. The ability to buffer energy abundance by storing lipids in adipose tissue is due to an adequate expansion of this tissue, which is a characteristic of adequate functionality of this tissue.

In fact, healthy white adipose tissue can dramatically expand, more than any other tissue, which occurs in response to changes in energy status and as a result of higher lipid deposit and a lower utilization rate. Adipose tissue can grow due to hyperplasia and hypertrophy.[30] Hyperplasia is an increase in the number of adipocytes and hypertrophy is an increase in the size of adipocytes. In physiological growth states such as adolescence and pregnancy, adipose tissue grows, mainly through hyperplasia. In adulthood, preadipocyte maturation capacity declines.[31] The expression of peroxisome proliferator-activated receptor gamma 2 (PPAR-γ), one of adipogenesis key regulators, has been shown to be higher in young individuals than in older adults.[32] Adipose tissue grows by hypertrophy as a result of the inability for maturating preadipocytes. Hypertrophic adipocytes are those that can release a higher concentration of free fatty acids and a larger proportion of pro-inflammatory adipokines.[33] This is accompanied by tissue blood flow changes and increased fibrotic process, which causes cell death.[34]

Finally, the dysfunctional adipose tissue hypothesis associates energy excess with cardiometabolic risk. For this reason, the scientific community has delved into the metabolism of adipose tissue in order to prevent such risks.

Brown adipose tissue

Adipose tissue brown coloration is due to the fact that it is more vascularized and has a high content of

mitochondria, which, in turn, have cytochromes, which are responsible for giving color. The fat cells that make up the brown adipose tissue are multilocular or have several lipid vacuoles. These cells have a polygonal shape and measure 15 to 50 µm.[31] Brown adipose tissue has a progenitor cell (positive for Myf5 expression) in common with skeletal muscle;[35] i.e., brown adipocytes do not stem from white adipocytes, but from muscle tissue precursor cells.

Unlike white adipose tissue, brown tissue does not have the function of storing energy, but it dissipates energy through thermogenesis. To achieve body temperature regulation, brown adipose tissue is localized in superficial and deep sites. In superficial sites, the interscapular, cervical and axillary regions are found, while in deep sites contain the perirenal, periaortic, inguinal and pericardial brown adipose tissues.[30] In humans, the interscapular, axillary and cervical regions acquire special importance (Fig. 1).

The presence of brown adipose tissue is especially clear in the neonatal stage. In fact, brown adipose tissue was long thought to be highly restricted in mass after birth. However, several recent studies have shown that brown adipose tissue in humans is represented by several metabolically active tissue structures.[36-38] Exposure to cold and overeating increases the activity and size of these structures, whereas age decreases them.[39] On the other hand, in rodents, brown adipose tissue is maintained throughout life and highly significantly contributes to energy expenditure by thermogenesis.[40]

β-adrenergic receptor activation in brown adipose tissue promotes the stimulation of uncoupling proteins (UCP), which use oxidative phosphorylation proton flow and thus produce heat instead of ATP. So far, three UCP isoforms have been identified and cloned: UCP1 and UCP2, which are expressed in white adipose tissue, while UCP3 is mainly expressed in brown adipose tissue and skeletal muscle.[41] It is in brown adipose tissue mitochondria where heat is produced by UCPs function and, as a consequence, energy expenditure is increased. When food is unavailable, hunger signals from the hypothalamus activate gabaminergic neurons, which block sympathetic system activation in order to decrease thermogenesis in brown adipose tissue and reduce energy expenditure.[42]

There is evidence that brown adipose tissue, like white adipose tissue, regulates energy homeostasis in response to overall metabolic status. In this regard, the description of the transdifferentiation or interconversion process has given clues about the possibility of white adipose tissue being transformed into brown. In adult animal models, fat mass in anatomical regions such as the epididymal and interscapular areas is known to be essentially composed of white and brown adipose tissue, respectively. However, in epididymal adipose tissue, the presence of brown adipocytes has been verified, whereas in interscapular adipose tissue, white adipocytes have been found.

There are conditions, such as a higher concentration of thyroid hormones, bile acids, natriuretic peptides and retinoids, that increase the number of brown adipocytes in white adipose tissue.[43] The development of brown adipocytes in white deposits has been associated with a lower risk for developing obesity and diabetes[44-47] and this is achieved with exposure to cold and with treatment with β-adrenergic receptor agonists.[48] In contrast, the conversion of brown into white adipocytes has been demonstrated in diet-induced obesity animal models.[49]

Probably by delving into the understanding of transdifferentiation, in the future there will be tools available that offer a preventive or therapeutic strategy for obesity.

Beige adipose tissue

Recently, adipose cells similar to brown adipocytes, with beige coloration and positive for UCP1 expression, were shown to be likely to appear in response to certain stimuli such as exercise, exposure to cold or some hormones.[50] They can accumulate in white adipose tissue typical deposits and have been called beige or “brite” adipocytes (a combination of the terms brown and white).

Although beige adipocytes have similar characteristics to the brown ones, such as their morphology (they contain several lipid vacuoles), they have different anatomical localizations. While beige adipocytes are immersed in the subcutaneous regions of white adipose tissue, brown adipocytes are essentially found in the aforementioned superficial regions (Fig. 1).

Brown and beige adipocytes appear to develop from different embryonic precursors.[51] As previously mentioned, brown adipocytes originate from Myf5-positive cells. In turn, beige adipose cells appear to descend from a Myf5-negative lineage,[52] although their exact origin is still under debate and two possibilities have been proposed: the first one suggests that they are derived from white adipocyte precursors and become beige adipocytes in response to environmental stimuli, such as exposure to cold; the second one proposes that mature white adipocytes can be transdifferentiated by having contact with the appropriate stimuli to become beige.[53] Finally, it is possible that both proposals are correct and that, depending on the environment,

genetic background and beige cell-containing adipose tissue localization, one or the other occurs.[54]

Under basal conditions, beige adipocytes express a signature of molecular markers that is similar to that of white adipocytes, but after transdifferentiation, they acquire an expression pattern similar to that of brown adipocytes. That is, a thermogenic expression pattern that reflects higher energy expenditure and oxygen consumption.[55]

Exercise is a stimulus that favors white adipose tissue transdifferentiation to beige adipose tissue. In 2012, a peptide released by skeletal muscle subjected to exercise in rodents was found to be able to influence on white adipose tissue "browning". In mouse white adipocyte cultures, this peptide turned the cells into UCP1-positive, with a beige phenotype; that peptide was named irisin;[56] it was observed to be present in the serum, and its concentration increases after short-term training. Circulating irisin increase resulted in a higher expression of mitochondrial genes and oxygen consumption in white adipose tissue. Since then, research on irisin has gained interest for the possible influence of this peptide on the metabolism of white adipose tissue and, therefore, on obesity.[57]

Adipose tissue color hues, what is the clinical reality?

As previously mentioned, brown and beige adipocytes share the ability to transform chemical energy into heat, thus contributing to adaptive thermogenesis. We know that the presence and activation of these cell types are not limited to the neonatal stage, but that can be induced in human adults.

In human adults, the most common areas of brown adipose tissue are supraclavicular and cervical.[58] The supraclavicular region appears to be abundant in brown and beige adipocytes, and its metabolic function has been established to be correlated with individual overall metabolic profile.[59]

Clinical trials have demonstrated that females have a larger mass of brown and beige adipose tissue in comparison with males, and that it is more active. It has also been established that the higher the adiposity, the lower the content and activity of brown and beige adipose tissue. Consistently, weight loss by bariatric surgery promotes an increase in the mass and function of brown adipose tissue.[60]

Actually, brown adipose tissue in humans is composed of a combination of multilocular brown or beige adipocytes and unilocular white adipocytes.[61] There is evidence that these adipose tissue deposits are waiting for environmental signals to "turn brown" and activate, as it was explained in animal models. Thus, hormones such as leptin, fibroblast growth factor 21, adrenergic hormones and some cytokines promote adaptive thermogenesis, by transdifferentiating white adipocytes in areas of brown adipose tissue and increasing their activation. As a result, the expression of UCP1 and other brown and beige adipose tissue markers is increased and energy expenditure is higher, which is accompanied by improved glucose tolerance.

Adaptive thermogenesis generated by cold or "shivering" is clearly accompanied by structural changes in the brown adipose tissue of humans, which affects energy homeostasis. For example, a change in room temperature from 24 to 19 and 17 °C increases brown adipose tissue mass, as well as energy expenditure, through an increase in the use of lipids and glucose.[62] Since physical activity and "shivering" simultaneously induce heat and irisin production in muscle tissue, the influence of this hormone on human white adipose tissue "browning" or transdifferentiation has been studied. Investigations are controversial. The conclusions of some studies show that physical training in human adults does not significantly increase irisin concentration, and neither does it promote an increased expression of genes related to adipose tissue "browning", such as UCP1, PGC-1b and PRDM16.[57] However, other investigations indicate that during exposure to cold, the secretion of irisin is proportional to the intensity of the "shivering" and similar to that induced by resistance exercise. The same group points out that irisin induces the conversion of human preadipocytes into beige adipocytes, while generating more heat by thermogenesis.[62]

Irisin and other signals appear to be responsible for causing adaptive thermogenesis and changing adipose tissue "color shades" in humans; however, this will have to be confirmed in the future. Nevertheless, it is clear that adipose tissue plasticity, its capacity for interconversion, transdifferentiation and "browning" offer an opportunity to modulate energy metabolism. Finally, the knowledge that is to be generated from the pathways that activate brown or beige adipose tissue might be used to establish therapeutic interventions to counteract insulin resistance and obesity.

Conclusions

The study of adipose tissue and its functions has provided valuable information for the understanding and possible treatment of the metabolic disorders that accompany obesity. White adipose tissue maintains metabolic homeostasis through adipokines or lipokines

regulated release. In turn, they respond to signals of the environment by promoting hunger or satiety, sensitivity or resistance to the action of insulin, lipid use or storage, inflammation or coagulation, among other processes. In white adipose tissue, areas with brown or beige cells that respond to physical activity or thermogenesis needs, which contribute to energy expenditure, both in animal and human models, can be generated. For this, the remodeling of adipose tissue is required, which results in a change in vascularization, inflammation, hypoxia, gene expression pattern and protein and lipid factors content. Finally, current knowledge on the colors of adipose tissue and its hues sheds light on the influence of global metabolism; in the future, we might have tools available for its modulation.

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REVIEW ARTICLE

National panorama of adolescent pregnancy in Mexico: lessons learned in a six-year period

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Abstract

Globally, adolescent pregnancy constitutes a serious public health problem of a multifactorial nature. Specifically for women, it entails various educational, economic and social implications that affect their life project and widen the social gaps in this age group. Furthermore, adolescent girls are more vulnerable because of the health risk involved with pregnancy at a younger age. According to the World Health Organization, "the probability of maternal death is twice as high in adolescents in comparison with women aged between 20 and 30 years, and for those younger than 15 years, the risks are five times higher". In general, adolescents are in great need for education on sexual and reproductive health issues, which should be aimed at increasing information and knowledge about correct use and access to modern contraceptive methods, as well as at demystifying fears and beliefs around their possible side effects. Ensuring proper counseling with trained personnel is equally vital. Public institutions have a social responsibility to support efforts aimed at preventing adolescent pregnancy, based on relevant lines of action and health policies.

KEY WORDS: *Adolescent pregnancy. Sexual health. Public health policies. Mexico.*

Panorama nacional del embarazo precoz en México: lecciones aprendidas en un sexenio

Resumen

En el mundo, el embarazo adolescente constituye un grave problema de salud pública de índole multifactorial. Específicamente para la mujer conlleva diversas implicaciones educativas, económicas y sociales que afectan su proyecto de vida y amplían las brechas sociales en este grupo etario. Asimismo, las adolescentes son más vulnerables por el riesgo en salud que implica un embarazo a corta edad; según la Organización Mundial de la Salud, "la probabilidad de muerte materna es dos veces más en las adolescentes respecto a las mujeres que se encuentran entre los 20 y 30 años de edad, y para las menores de 15 años los riesgos son cinco veces mayores". En general, las y los adolescentes experimentan una gran necesidad de educación en temas sobre salud sexual y reproductiva, la cual debe dirigirse al aumento de información y conocimientos sobre el uso correcto y acceso a métodos anticonceptivos modernos, así como a desmitificar los temores y creencias en torno a sus posibles efectos secundarios. Asegurar una consejería adecuada y con personal capacitado es igualmente vital. Las instituciones públicas tienen la responsabilidad social de respaldar los esfuerzos encaminados a prevenir el embarazo adolescente, con base en las líneas de acción y políticas sanitarias.

PALABRAS CLAVE: *Embarazo adolescente. Salud sexual. Políticas de salud pública. México.*

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Introduction

According to figures from the World Health Organization, approximately 16 million adolescents aged 15 to 19 years and one million girls younger than 15 give birth each year,[1] most of them in countries like Mexico, considered by the World Bank as having a middle-income economy, and in countries with high poverty and marginalization rates.[2]

Globally, complications during pregnancy and delivery are the second cause of death among adolescents. Annually, around three million young females with unwanted pregnancies undergo unsafe abortions, practiced under risky conditions by untrained personnel.[3] Even when since 1990 there has been a considerable decrease in adolescent fertility rates worldwide, this reduction has been irregular and 11 % of all births are estimated to still occur in girls or female adolescents, out of which 95 % live in countries with middle and low human development rates. In 2014, global average fertility rate among female adolescents aged 15 to 19 years was 49 per 1000.

According to estimates of the National Population Council (Conapo – *Consejo Nacional de Población*) for 2015 and 2019, age-specific fertility rate (ASFR, defined as the number of births per thousand women in an age group) in adolescents aged 15 to 19 years corresponded to the international indicator Mexico is committed to in the framework of the Sustainable Development Goals[4] and at the Montevideo Consensus.[5] In 2015, the ASFR figure among adolescents aged 15 to 19 years was 74.3, and it is estimated that in 2019 final count it will be 69.5. The source of this information comes from Conapo preliminary estimates based on the 2016-2050 Population Projections.[6] Adolescent fertility estimates for girls aged 10 to 14 years constitute a methodological challenge, since the measure used is not a rate, but a ratio. This is because it is assumed that the majority of girls aged 10 and 11 do not yet have their first menstruation (denominator), and therefore they cannot be considered as being exposed to the risk of pregnancy.

The fertility ratio and rate in girls and female adolescents aged 10 to 14 and 12 to 14 years, approved by Inter-Institutional Group for the Prevention of Adolescent Pregnancy[7] to monitor the magnitude of births in girls younger than 15 years, are not figures that are officially used but as a mechanism for follow-up and evaluation of the National Strategy for Adolescent Pregnancy Prevention.[8] The prevention and intervention efforts carried out by different government branches are vast and innovative; however, adolescent pregnancy is a phenomenon where complex variables intersect and often do not respond to successful strategies that have been implemented to combat other health problems.

The adolescent pregnancy epidemic has been studied in a fragmented manner as a consequence of the gender inequality that adversely affects girls and female adolescents living in rural communities or metropolitan periurban areas of high marginalization.[9] The adolescent pregnancy epidemic is the result of various problems, including:

- The quality of the education that is offered to young people, which does not allow them to design an ambitious life plan where reproduction is postponed for later ages;[10]
- A socio-cultural environment where motherhood is seen as a value that exceeds academic, professional or personal achievements;[11]
- Lack of real access to contraceptive methods that young females can use and to evidence-based knowledge, including last-generation reversible methods designed for nulliparous women.[12]
- Intergenerational transmission of poverty, whereby behavioral patterns are especially replicated from mothers to daughters;[13]
- Reproductive coercion,[14] another manifestation of gender-based violence, and the sexual harassment or violence that young women suffer daily within their homes and in their environment,[15] which limits their capacity to negotiate safe sex.
- The fact that the lower the reproductive age, the lesser the spacing of children and the larger the number of male partners that support women to provide for their families.[16]

The biological and social consequences of adolescent pregnancy include the following:

- A higher mortality rate during delivery and postpartum,[17] as a result of undernourishment, obesity or overweight before, during and after delivery.[18]
- Children with low birth weight.[19]
- Increase in the number of households headed by women,[20] which are historically poorer.
- Illiteracy, which is more common in females.[21]
- An explosion in the use of social networks among young females, which presents an aspirational image that hardly finds an objective translation in their daily living.[22]

All this, coupled to a lack of political will of some groups and the conservatism of factual powers,[23] which

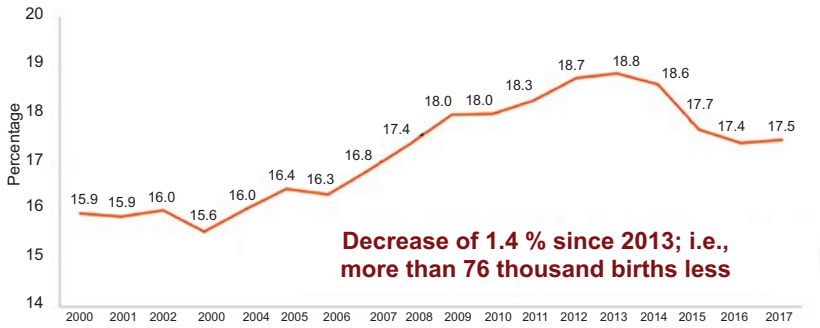

Figure 1. *Percentage of births in child and adolescent mothers (younger than 20 years), Mexico, 2000-2017. Source: INEGI. Births per registration year according to maternal age at birth, including mothers with habitual residence abroad, 2019.*

prevent young females and women from exercising their constitutional right to a life free of violence,[24] from having access to a wide range of methods for family planning[25] offered by duly trained health personnel in youth-friendly services,[26] including voluntary termination of pregnancy (VTP) within the first 20 weeks of gestation when the pregnancy is the result of rape or sexual violence, or termination of pregnancy within the first 12 weeks for other reasons, which is a procedure that was decriminalized in Mexico City in April 2007 and that can be performed legally, safely and free of charge in Mexico City's Ministry of Health facilities.[25,27]

Since 2003, access to legal and safe abortion has been a priority for the World Health Organization.[3,28] The Latin American and Caribbean region has the most restrictive abortion legislation,[29] even when compared to the legislation in force in Sub-Saharan Africa. Adolescent pregnancy is the result of the aforementioned social, cultural, educational and historical determinant factors, and has consequences that have not been systematically explored, such as the risk to the health of the mother-child binomial, at early stages of life, and in the course of adulthood.[30] Another important association is that which links early pregnancy with maternal metabolic status, since a high incidence of metabolic syndrome has been identified in Mexican women, with reports suggesting that early pregnancy increases this risk.[31]

World situation and the case of Mexico

Pregnancy in girls and female adolescents, a problem that affects practically the entire world, also causes more than 70,000 deaths due to complications associated with pregnancy and childbirth, with at least 3.2 million unsafe abortions being estimated to occur.[32]

In Mexico alone, more than 2.2 million births were recorded in 2017, out of which 17.5 % occurred in females aged between 10 and 19 years, i.e. slightly more than 390,000, out of which 9748 were the result of conception in girls aged between 10 and 14 years.[33]

Institutional response

In view of this panorama, the World Health Organization has proposed various strategies to address the problem, including the limitation of marriage before 18 years of age, an increase in the offer of family planning methods, a reduction of unsafe abortions and an increase of skilled care before, during and after delivery.[34]

In Mexico, the National Strategy for the Prevention of Pregnancy in Adolescents was launched in January 2015, whose main objective is to reduce the number of adolescent pregnancies in Mexico with absolute respect for human rights, particularly sexual and reproductive rights, and reach two measurable goals by 2030: to reduce birth rates in girls aged 10 to 14 years to zero, and to reduce age-specific fertility rate in adolescent females aged 15 to 19 years by 50 %. Figures 1 to 3 show the trend of births in child and adolescent mothers during the 2000-2017 period.

The National Population Council (Conapo) was entrusted with the task of coordinating the strategy, where different government entities participated: the Ministries of Health, Public Education, Social Development, the National Women's Institute and social security institutions.

Various actions were proposed, including the creation of the Inter-institutional Group for the Prevention

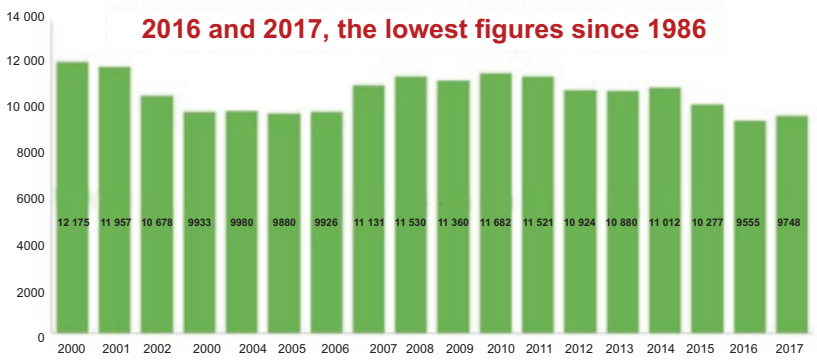

Figure 2. *Births in mothers younger than 15 years, Mexico, 2000-2017. Source: INEGI. Births per registration year according to maternal age at birth, including mothers with habitual residence abroad, 2019.*

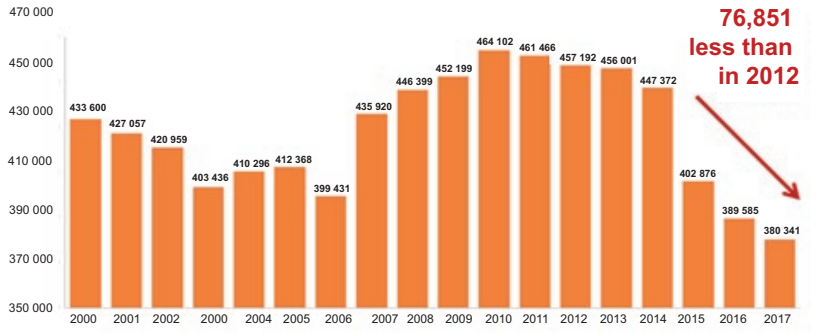

Figure 3. *Births in mothers aged 15 to 19 years, Mexico, 2000-2017. Source: INEGI. Births per registration year according to maternal age at birth, including mothers with habitual residence abroad, 2019.*

of Pregnancy in Adolescents (as a technical coordination central element), the training of human resources that were responsible for making the operational translation of the strategy, strengthening of Adolescent-Friendly Services, centralized purchase of contraceptives, focalization of actions, and dissemination and evaluation of the strategy. The Model of Comprehensive Care of Sexual and Reproductive Health for Adolescents (MAISSRA – *Model de Atención Integral a la Salud Sexual y Reproductiva*) was also developed and published. Below, some of the referred actions are described.

Training

Various face-to-face and distant activities were carried out to train personnel, mainly health personnel, in the application of the MAISSRA and the *Official Mexican Standard NOM-047-SSA2-2015, for the health care of the group aged from 10 to 19 years*, a complicated task due to the multiplicity of stakeholders and participants.

Adolescent-friendly services

Over the last six years, these services did increase by 146.9 %. By December 2018, there were 2605; 83.6 % of all municipalities in the country have at least one friendly service; in 2017 and 2018, more than 900 thousand adolescents were provided care annually in friendly services, between two and three events of care a year per adolescent.

A significant attendance of children younger than 15 years and adolescent males has been observed; the most demanded services are guidance-counseling, prevention and care of sexually transmitted infections and prescription of contraceptives.[35]

It should be noted that these services are looked after by doctors, nurses or psychologists, but the presence of trained young people who support the operation of friendly services is highly relevant.

Purchase of contraceptives

The decision was made to centralize the purchases of family planning supplies, given that some states were not acquiring them. Between 2014 and 2018, more than 4 billion pesos were invested for this purpose, and although not all health units were necessarily reached with all the acquired methods, their supply was increased. Between 12 and 14 item keys (different methods) were made available to state health services, according to a planning exercise where the population to be protected and the health units where they were to be distributed, among other issues, were considered. From condoms to long-acting reversible contraception methods (e.g., implants) were acquired.

Focalization

All 32 states prioritized pregnancy prevention strategies in girls and female adolescents in 200 municipalities and 135 health jurisdictions, which comprised 56.3 % of females aged 15 to 19 years and covered 54.1 % of total live births in mothers aged 10 to 14 years and 57.9 % of live births in mothers aged 15 to 19 years; 89 % of the 200 priority municipalities had at least one Adolescent-Friendly Service.

Conclusions

In Mexico, the demographic bonus lost for a country,[36] as well as the long-term metabolic, neurocognitive and social consequences that are documented, converge in adolescent pregnancy. It is mandatory and urgent to design educational health interventions and cultural norms with an emphasis on adolescent girls life plan. These interventions should be early, evaluated, replicable and sustainable throughout the country. Adolescent pregnancy continues to be one of the main factors that contribute to maternal and child mortality and to perpetuate the circle of disease and poverty. Not addressing this problem is to underpin a form of planned poverty.[37]

There has been an institutional response that has to be evaluated and, if necessary, modified. Some encouraging, although insufficient, achievements have been obtained. It is desirable to continue with that, which after being assessed, shows a positive contribution to address the problem, and to modify or eliminate everything that does not have an impact on the reduction of adolescent pregnancies.

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ORIGINAL ARTICLE

Complications in pregnancies achieved by assisted reproduction

*José M. Madrazo-Cabo, Grecia A. León-Durán, Adriana Oliveros-Montiel, José A. Ledesma-Montes, Iván D. Morales-González and VirginiaSedeño-Monge**

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Abstract

Introduction: *Pregnancies resulting from assisted reproductive technologies (ART) have been documented to have a higher risk of adverse effects.* **Objective:** *To provide evidence on obstetric and perinatal complications associated with conceptions by ART versus spontaneous pregnancies.* **Method:** *Comprehensive review of original articles published between 2010 and 2018 addressing the more common obstetric and perinatal complications in pregnancies resulting from in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), in comparison with spontaneous conceptions.* **Results:** *Thirty-seven original articles, which reported on 26 cohort studies and 11 case-control trials, were included. IVF and ICSI conceptions were associated with a larger number of obstetric and perinatal complications such as low birth weight, prematurity, low weight for gestational age, admission to the neonatal intensive care unit, congenital malformations, C-sectionand premature rupture of membranes, among others.* **Conclusions:** *Pregnancies by ART are associated with an increased risk of obstetric and perinatal complications in comparison with spontaneous conceptions. Further research is needed to determine which aspects result in higher risk.*

KEY WORDS: *Assisted human reproduction. In vitro fertilization. Intracytoplasmic sperm injection.*

Complicaciones en embarazos logrados por reproducción asistida

Resumen

Introducción: *Se ha documentado que los embarazos por técnicas de reproducción asistida (TRA) presentan mayor riesgo de efectos adversos.* **Objetivo:** *Proporcionar evidencia actualizada de las complicaciones obstétricas y perinatales asociadas con concepciones mediante TRA versus embarazos espontáneos.* **Método:** *Revisión de artículos originales publicados entre 2010 y 2018, que abordan complicaciones obstétricas y perinatales de mayor frecuencia en embarazos por fertilización in vitro (FIV) e inyección intracitoplasmática de espermatozoides (ICSI) comparados con concepciones espontáneas.* **Resultados:** *Se incluyeron 37 artículos originales, 26 de cohorte y 11 de casos y controles. Las concepciones por FIV e ICSI se asociaron con más complicaciones obstétricas y perinatales como bajo peso al nacimiento, prematuridad, menor peso para la edad gestacional, ingreso a la unidad de cuidados intensivos neonatales, malformaciones congénitas, cesárea, ruptura prematura de membranas, entre otras.* **Conclusiones:** *Las concepciones por TRA se asocian con mayor riesgo de complicaciones obstétricas y perinatales en comparación con las espontáneas. Es necesario realizar estudios adicionales que determinen qué aspectos derivan en mayor riesgo.*

PALABRAS CLAVE: *Reproducción humana asistida. Fertilización in vitro. Inyección intracitoplasmática de espermatozoides.*

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Introduction

Each year, more than 200,000 babies are born worldwide as a result of the use of assisted reproductive technologies (ART);[1,2] to date, approximately 7 million children conceived through this modality have been born.

In in vitro fertilization (IVF), the ovaries are stimulated with medications and are subsequently aspirated from the ovarian follicles and fertilized in vitro; the retrieved oocytes are mixed with sperm in a culture medium, and then are transferred to the uterine cavity.[3]

As part of an IVF cycle, a single sperm is injected into the cytoplasm of a mature oocyte (intracytoplasmic sperm injection, ICSI), which is an efficacious method to help fertilization in men with suboptimal semen parameters or with low fertilization rates.

As experience was accumulated, success rates increased and indications for these procedures were expanded, with little formal evaluation of their effects on maternal and fetal well-being.[4] Several studies have indicated that ART can generate a higher risk of maternal and perinatal complications in comparison with spontaneous conceptions.[5]

Method

A review of original articles published in indexed journals such as PubMed, Medline, CONRICyT, Medigraphic and SciELO between 2010 and 2018 was carried out. The keywords used were “assisted reproductive techniques”, “in vitro fertilization”, “IVF”, “intracytoplasmic sperm injection”, “ICSI”, “perinatal outcomes” and “obstetric outcomes”. Articles comparing obstetric and perinatal complications between IVF and ICSI pregnancies and spontaneous conceptions, both cohort and case-control studies, were included. Meta-analyses, systematic reviews and articles not having spontaneous pregnancies as a control group were excluded.

Results

Thirty-seven trials were included, out of which 26 were cohort and 11 case-control studies. Data on each study are shown in Table 1.

The results are described according to the type of complication and to the type of articles in which the relative risk of finding these complications was statistically higher ($p < 0.05$) in ART-induced pregnancies versus spontaneous conceptions.

Complications

- *Prematurity:* complication reported in 26 articles (70 % of total), in 67,186 pregnancies resulting from IVF-ICSI; gestational age recorded at birth ranged from 32 to 37 weeks. In 18 articles, the frequency of prematurity was significantly higher with ART in comparison with spontaneous pregnancies.[6-23]
- Low birth weight: this complication was reported in 21 articles (59,140 ART-related births) (57 % of total). Less than 2,500 g was considered low birth weight, and less than 1,500 g was regarded as very low weight; in five articles, significant values were reported for very low weight[6,12,17,18,22] and in 14 for low weight in pregnancies resulting from ART, in comparison with spontaneous pregnancies.[6,8,9,12,13,16-19,22,24-27]
- *Perinatal mortality:* this complication is defined as intrauterine death of a fetus weighing less than 500 g or having less than 20 weeks of gestational development and that of neonates within the first seven days of life.[9,18,28,29] Out of 18 articles (49 % of total) that included 591 pregnancies resulting from IVF-ICSI and in which perinatal mortality was reported, seven recorded significant mortality values in ART pregnancies in comparison with spontaneous pregnancies.[12,17,18,22,23,30,31]
- *Small for gestational age (SGA):* it is defined as a child with birth weight below the 75th percentile[28] or weighing less than 2 standard deviations than the population for that gestational age.[17] In 13 articles (35 % of total) that included 10,631 IVF-ICSI, this complication was reported; in four, the result was significant.[12,17,24,32]
- *Admission to the neonatal intensive care unit (NICU):* this complication was reported in eight articles that included 604 IVF-ICSI; five studies showed significant difference in pregnancies obtained by means of ART.[9,18,19,22,23]
- *Congenital malformations:* Twenty articles (54 % of total), which included 7288 IVF-ICSI procedures, report congenital malformations; cardiovascular malformations were the most common in 10 articles. In comparison with spontaneous conceptions, an increased trend to find any congenital defect was reported in pregnancies

Table 1. Characteristics of studies published in indexed journals between 2010 and 2018 addressing obstetric and perinatal complications between pregnancies resulting from IVF and ICSI and spontaneous conceptions

Study	Country, period	Design	Population	Reported complications
Bassioun et al., 2014[23]	Egypt, January 2010-December 2012	Case-control	Cases: 739 ICSI Controls: 843 spontaneous pregnancies	The ICSI group was associated with a higher incidence of twins 12.7 % ($p < 0.001$), premature delivery 3.8 % ($p = 0.022$), PROM 4.6 %($p = 0.001$), C-section 74.1 % ($p < 0.001$) and neonatal deaths 10.4 % ($p < 0.001$)
Boulet et al., 2016[35]	United States, 2000-2010	Retrospective cohort	Exposed cohort: 64,861 IVF-ICSI Non-exposed cohort: 4,553,215 spontaneous pregnancies	The prevalence of one or more non-chromosomal defects was 58.59/10,000 children conceived with ART (n = 389) versus 47.50/10,000 in children conceived without ART (n = 22,036); aOR = 1.28, 95 % CI = 1.15-1.42
Caserta et al., 201[49]	Italy, January 2007-June 2011	Case-control	Cases: 138 IVF-ICSI Controls: 207 spontaneous pregnancies	Gestational age and birth weight were lower in the ART group. The frequency of diabetes and placental abruption was higher for ART in comparison with spontaneous pregnancies. Pregnancies by ART had a higher incidence of placental abruption (OR = 7.45, 95 % CI = 2.05-26.98) and patent ductus arteriosus (OR = 3.39, 95 % CI = 1.01-11.46).
Farhi et al., 2013[20]	Israel, June 2006-December 2008	Prospective cohort	Exposed cohort: 561 ART (223 IVF and 338 ICSI) Non-exposed cohort: 600 spontaneous pregnancies.	Pregnancies through IVF were associated with prematurity (OR = 2.36, 95 % CI = 1.28-4.37) and low birth weight (OR = 1.89, 95 % CI = 1.03-3.46)
Farhi et al., 2013[21]	Israel, 1997-2004	Retrospective cohort	Exposed cohort: 9042 IVF-ICSI Non-exposed cohort: 213,288 spontaneous pregnancies	Higher risk of CM with ART (2.4 % versus 1.9 %, aOR = 1.45, 95 % CI = 1.26-1.68). In single NBs, the risk for nervous system disorders was increased (OR = 2.13, 95 % CI = 1.04-4.37), as well as for circulatory system (OR = 1.47, 95 % CI = 1.09-1.98), digestive system (OR = 3.10,95% CI = 1.48-6.48) and genital apparatus disorders (OR = 1.60, 95 % CI = 1.0-2.52), in the group of ART pregnancies versus spontaneous pregnancies
Harlev et al., 2018[15]	Israel, January 1991 -December 2013	Case-control	Cases: 229 IVF Controls: 7929 spontaneous pregnancies	Preterm delivery ($p < 0.001$), growth restriction ($p < 0.001$) and C-section ($p < 0.001$) had high prevalence in pregnancies resulting from ART (IVF)
Healy et al., 2010[42]	Australia, 1991-2004	Retrospective cohort	Exposed cohort: 6730 IVF-ICSI. Non-exposed cohort: 24,619 spontaneous pregnancies	The IVF-ICSI group had a higher incidence of postpartum hemorrhage (6.7 % versus 3.6 %, aOR = 2.0, 95 % CI = 1.8-2.3)
Henningsen et al., 2011[16]	Denmark, 1994-2008	Retrospective cohort	Exposed cohort: 3881 IVF-ICSI Non-exposed cohort: 7758 spontaneous pregnancies	Higher risk of LBW (OR = 1.4, 95 % CI = 1.1-1.7) and prematurity (OR = 1.3, 95 % CI = 1.1-1.6) with IVF-ICSI in comparison with spontaneous pregnancies
Jackson et al., 2015[38]	United States, January 2000-October 2010	Retrospective cohort	Exposed cohort: 185 IVF Non-exposed cohort: 193 spontaneous pregnancies	Increased risk of placenta accreta (2.7 % versus 0 %) and elective C-section (75.1 % versus 49.7 %) in women who conceived by means of ART in comparison with those with spontaneous pregnancy
Källen et al., 2010[6]	Sweden, 1982-2007	Retrospective cohort	Exposed cohort: 1545 twins by IVF. Non-exposed cohort: 8675 spontaneous twins	Higher risk of premature birth < 32 WOG (aOR = 1.52, 95 % CI = 1.18-1.97), LBW < 500 g (OR = 1.54, 95 % CI = 1.25-1.89) in the IVF group
Källén et al., 2010[37]	Sweden, 1982-2007	Case-control	Cases: 15,570 IVF Controls: 689,157 spontaneous pregnancies	Increased risk of congenital malformations (OR = 1.23, 95 % CI = 1.14-1.32) associated with IVF
Kosteria et al., 2017[39]	Greece	Case-control	Cases: 42 ICSI. Controls: 42 spontaneous pregnancies	The ICSI group had a shorter gestation, more C-sections ($p = 0.003$), lower birth weight and length

(*Continues*)

Table 1. Characteristics of studies published in indexed journals between 2010 and 2018 addressing obstetric and perinatal complications between pregnancies resulting from IVF and ICSI and spontaneous conceptions (*Continued*)

Study	Country, period	Design	Population	Reported complications
Lerner-Geva et al., 2017[27]	Israel, 1994-2004	Historical cohort	Exposed cohort: 9042 IVF Non-exposed cohort: 211,763 spontaneous pregnancies	Children conceived with ART had a significant risk for specific cancer such as retinoblastoma (OR = 6.18, 95 % CI = 1.22-31.2) and renal tumors (OR = 3.25, 95 % CI = 1.67-6.32)
Messerschmidt et al., 2010[32]	Austria, 1999-2007	Retrospective cohort	Exposed cohort: 195 IVF Non-exposed cohort: 1228 spontaneous pregnancies	Preterm births were more common in multiple pregnancies obtained by IVF (81.8 %) unlike spontaneous pregnancies (57.2 %) and SGA (p < 0.01)
Min Yang et al., 2018[31]	China, 2006-2016	Retrospective cohort	Exposed cohort: 2484 IVF Non-exposed cohort: 109,559 spontaneous pregnancies	ART conceptions had a higher risk for any type of birth defect in comparison with spontaneous pregnancies (aOR 2.10, 95 % CI = 1.63–2.69)
Moini et al., 2012[18]	Iran, January 2008-October 2010	Prospective cohort	Exposed cohort: 420 IVF Non-exposed cohort: 340 spontaneous pregnancies	Preterm birth rates (OR = 5.2, 95 % CI = 2.1-12.9), LBW (OR = 2.2, 95 % CI = 1.0-3.9), NICU admission (OR = 2.0, 95 % CI = 1.2-3.2) and perinatal mortality (OR = 2.3, 95% CI = 1.2-4.0) were significant for ART
Mozafari Kermani et al., 2018[36]	Iran, January 2012-december 2014	Historical cohort	Exposed cohort: 168 IVF-ICSI. Non-exposed cohort: 652 spontaneous pregnancies	Children conceived with ART had twice the risk of CM (p = 0.046) in comparison with those conceived by spontaneous pregnancy
Opdahl et al., 2015[43]	Sweden, Denmark and Norway, 1988-2007	Retrospective cohort	Exposed cohort: 58,006 IVF-ICSI Non-exposed cohort: 315,273 spontaneous pregnancies	The risk of hypertensive disorders of pregnancy was higher in the ART group (OR = 1.16, 95 % CI = 1.10–1.21)
Panagiotopoulou et al., 2016[34]	Greece, 1995-2012	Retrospective cohort	Exposed cohort: 389 IVF-ICSI. Non-exposed cohort: 485 spontaneous pregnancies	In the ART group, 8.2 % had congenital cardiovascular disease in comparison with 4.3 % of those naturally conceived (OR = 1.90, 95 % CI = 1.08-3.34, p = 0.024)
Pelkonen et al., 2014[11]	Finland, 1995-2006	Retrospective cohort	Exposed cohort: 4772 IVF. Non-exposed cohort: 31 243 spontaneous pregnancies	Children of ART pregnancies had a higher risk of major CM (OR = 1.24, 95 % CI = 1.05-1.47) in comparison with those spontaneously conceived
Poon et al., 2013[22]	Singapore, November 2001-January 2012	Retrospective cohort	Exposed cohort: 536 IVF-ICSI Non-exposed cohort: 16,335 spontaneous pregnancies	ART pregnancies were associated with higher risk of prematurity (OR = 5.95, 95 % CI = 4.99-7.08), LBW (OR = 5.54, 95 % CI = 4.37–6.13) and perinatal mortality (OR = 4.33, 95 % CI = 2.05-9.12)
Raatikainen et al., 2012[19]	Finland, 1989-2007	Case-control	Cases: 428 IVF/ICSI. Controls: 18,984 spontaneous pregnancies	ARTs significantly increased the risks of preterm birth (OR = 2.72, 95 % CI = 1.02-7.22) and LBW (OR = 1.92, 95 % CI = 1.31-2.81)
Sazonova et al., 2011[17]	Sweden, 2002-2006	Retrospective cohort	Exposed cohort: 13,544 IVF Non-exposed cohort: 587,009 without ART	IVF was associated with a higher risk of prematurity < 28 WOG (aOR = 1.69, 95 % CI = 1.34-2.14), LBW < 2500 g (aOR = 1.91, 95 % CI = 1.79-2.04) and weight <1500 g (aOR = 1.72, 95 % CI = 1.49-1.99) in comparison with spontaneous pregnancy
Sazonova et al., 2012[40]	Sweden, 2002-2006	Retrospective cohort	Exposed cohort: 11,292 IVF Non-exposed cohort: 571,914 spontaneous pregnancies	ARTs were related to a higher rate of prematurity (aOR = 1.92, 95 % CI = 1.12-3.93), macrosomia (aOR = 1.29, 95 % CI = 1.04-1.59) and preeclampsia (aOR = 1.25, 95% CI = 1.03- 1.51) in comparison with spontaneous pregnancies
Sun et al., 2014[8]	China, 2004-2008	Case-control	Cases: 1327 IVF/ICSI Controls: 5222 spontaneous pregnancies	The ART group had a higher incidence of C-section (OR = 1.40; 95 % CI = 1.24-1 .60), prematurity and low birth weight (p < 0.001)

(*Continues*)

Table 1. Characteristics of studies published in indexed journals between 2010 and 2018 addressing obstetric and perinatal complications between pregnancies resulting from IVF and ICSI and spontaneous conceptions (*Continued*)

Study	Country, period	Design	Population	Reported complications
Sundh et al., 2014[59]	Sweden, Denmark, Finland and Norway, 1982-2007	Retrospective cohort	Exposed cohort: 91,796 IVF-ICSI Non-exposed cohort: 358,419 spontaneous pregnancies	An increased risk was observed for two out of 12 types of cancer in the ART group: CNS tumors, aOR = 1.44 and 95 % CI = 1.01-2.05 and malignant epithelial neoplasms, aOR = 2.03 and 95 % CI = 1.06-3.89
Suzuki et al., 2010[25]	Japan, 2000-2007	Case-control	Cases: 64 IVF Controls: 87 spontaneous pregnancies.	The C-section rate in the IVF group was higher (86 %) than in the control group (67 %), with the difference being statistically significant (p < 0.01)
Tomic et al., 2011[60]	Croatia, 2006-2009	Case-control	Cases: 283 IVF. Controls: 283 spontaneous pregnancies.	Singleton pregnancies with IVF in primiparous women ≥ 35 years had a higher number of C-sections in comparison with spontaneous pregnancies (p < 0.0001) and LBW (p < 0.05)
Toshimitsu et al., 2014[26]	Japan, 2006-2010	Case-control	Cases: 88 IVF-ICSI Controls: 242 spontaneous pregnancies	Statistically significant increase in gestational hypertension with ART (p < 0.002)
Valenzuela-Alcaraz et al., 2018[33]	Spain, 2014 - 2016	Prospective cohort	Exposed cohort: 50 IVF-ICSI Non-exposed cohort: 50 spontaneous pregnancies	ART twin fetuses showed significant cardiovascular changes with a predominance of right heart disease (p < 0.001)
Wen et al., 201028	Canada, 1996-2005	Retrospective cohort	Exposed cohort: 1044 IVF-ICSI Non-exposed cohort: 1910 spontaneous pregnancies	ARTs were related to a higher risk of preeclampsia (aOR = 2.15, 95 % CI = 1.33-3.46) and a higher number of cardiac CM in comparison with spontaneous pregnancies (aOR = 4.58, 95 % CI = 1.48-14.18)
Wennberg et al., 2016[12]	Sweden, Denmark, Finland and Norway 1982-2007	Retrospective cohort	Exposed cohort: 39,890 IVF-ICSI Non-exposed cohort: 245,600 spontaneous pregnancies	The risk of prematurity, LBW, CM, SGA, fetal death, C-section and obstetric hemorrhages was higher in the ART group than in the group of spontaneous pregnancies (p < 0.001)
Wisborg et al., 2010[7]	Denmark, 1989-2006	Prospective cohort	Exposed cohort: 742 IVF-ICSI Non-exposed cohort: 18,473 spontaneous pregnancies	Statistically significant increase in preterm birth < 37 WOG (OR = 1.53, 95 % CI = 1.15–2.04) and < 32 WOG (OR = 2.33, 95 % CI = 1.17–4.65) in IVF-ICSI compared to fertile women
Wisborg et al., 2010[30]	Denmark, 1989-2006	Prospective cohort	Exposed cohort: 730 IVF-ICSI Non-exposed cohort: 18,545 spontaneous pregnancies	IVF-ICSI pregnancies were associated with an increased risk of fetal death (aOR = 4.08, 95 % CI = 2.11-7.93)
Yang et al., 2014[10]	China, January-December 2011	Case-control	Cases: 1139 IVF-ICSI Controls: 111,264 spontaneous pregnancies	The IVF-ICSI pregnancy group had a higher incidence of HBP (OR = 1.27. 95 % CI = 1.04-1.60), premature delivery (OR = 4.53, 95 % CI = 3.91-5.25), gestational diabetes (OR = 3.05, 95 % CI = 2.57-3.60) and placenta previa (OR = 2.18, 95 % CI = 1.62-2.94)
Yu HT et al., 2018[13]	China, 2005-2016	Retrospective cohort	Exposed cohort: 6372 IVF-ICSI Non-exposed cohort: 2,182,179 spontaneous pregnancies	High risk of prematurity (p = 0.025), LBW < 2,500 g and < 1,500 g (p < 0.001) in the ART group
Zhu et al., 2016[24]	China, 2006-2014	Retrospective cohort	Exposed cohort: 2641 IVF-ICSI Non-exposed cohort:5282 spontaneous pregnancies	ART pregnancies were associated with a higher risk of gestational diabetes (OR = 1.99, 95 % CI = 1.69-2.36), gestational hypertension (aOR = 2.58, 95 % CI = 2.11-3.15), placenta previa (OR = 2.23, CI 95 % = 1.79-2.78), postpartum hemorrhage (OR = 2.72, 95 % CI = 2.18-3.41) and placental adhesions (OR = 2.37, 95 % CI = 1.90-2.95).

aOR= adjusted odds ratio, ART = assisted reproductive technologies, BMI = body mass index, CI = confidence interval, CM = congenital malformations, DM = diabetes mellitus, ICSI = intracytoplasmic sperm injection, IVF = in vitro fertilization, HBP = high blood pressure, LBW = low birth weight, NB = newborn, NICU = neonatal intensive care unit, OR = odds ratio, PROM = premature rupture of membranes, SGA = small for gestational age, WOG = weeks of gestation.

achieved with ART. The difference was significant in seven studies.[11,13,21,27,28,31,33-37]

- *Cesarean section:* Twenty-three articles, where 47,482 conceptions by IVF-ICSI were recorded, reported elective or emergency C-section, which accounted for 52 % of the complications. In 14 studies, the indication for C-section was significant in pregnancies resulting from ART when compared with spontaneous pregnancies.[8-10,12,15,19,22,23,25,33,34,38-40]
- *Premature and preterm rupture of membranes:* Premature rupture of membranes (PROM) is defined as the rupture of membranes prior to the start of labor; it is called preterm when it occurs before 37 weeks of gestation.[41] Nine articles (24 % of total) informed on PROM and preterm PROM (1322 ART conceptions), three indicated significant results in comparison with spontaneous pregnancies.[17,23,24]
- *Obstetric hemorrhage:* obstetric hemorrhage was regarded as bleeding due to placenta previa or premature placental abruption, a complication recorded in 13 articles (35 % of total), which included 2110 pregnancies resulting from IVF-ICSI. In five studies, the results were significant when compared with those of spontaneous pregnancies.[9,12,22,24,42]
- *Gestational diabetes:* it was reported in 17 articles (46 % of total), which included 1455 IVF-ICSI pregnancies; five reported significant results in the comparison with spontaneous pregnancies.[9,10,22,24,31]
- *Hypertensive disorders of pregnancy:* these conditions included gestational hypertension, preeclampsia and eclampsia, and were recorded in 19 studies (51 % of total), which included 8416 IVF-ICSI; these disorders were one of the most common complications. Only 11 articles indicated significant risk in comparison with spontaneous pregnancies.[9,10,12,22,24,26,28,31,33,40,43]

Discussion

Complications in IVF multiple gestations have been suggested to be similar to those occurring in spontaneous conceptions; however, IVF singleton pregnancies are associated with a higher incidence of complications.[44,45] The exact reasons for this increase are not clear, but potential factors include maternal and paternal characteristics, underlying medical conditions associated with subfertility and infertility, sperm factors, use of fertility drugs, laboratory conditions during embryo culture, culture medium, cryopreservation and thawing, prenatal genetic diagnosis (if performed), differences in obstetric management or a combination of the above factors.[46]

In the presented research, 26 cohort and 11 case-control articles were analyzed, which included 10,717,574 births; 351,217 pregnancies resulting from ART and 10,366,357 spontaneous pregnancies.

The most common perinatal complications were prematurity and low birth weight. The most important risk factor for preterm birth has been referred to be multiple gestation, which originates in a higher proportion in ART pregnancies. In addition, a higher incidence of premature births has been identified in ART singleton deliveries in comparison with children conceived in single spontaneous pregnancies.[47] As for maternal complications, a high proportion of C-section indications and hypertensive disorders of pregnancy was detected; the former might be related to anxiety and decision of the doctor given the conditions of the pregnancy.[48]

Elective C-section increases morbidity and mortality in comparison with vaginal delivery[49] and represents a risk of maternal-fetal complication, since it is associated with hemorrhage, infections, injury to adjacent organs and venous thromboembolism, among other maternal consequences.[50] Transient tachypnea, respiratory distress and immune response impairment can occur in neonates.[51]

Although gestational diabetes is significantly associated with factors such as obesity,[52] body mass index > 30,[53] age > 35 years, insulin resistance and elevated triglyceride levels,[54] five articles reported that the risk of experiencing it was significantly higher in ART pregnancies, in comparison with spontaneous conceptions.

Congenital cardiovascular malformations were the most common malformations, similar to that which was reported in another research.[55]

One strength of our work was the period that was examined (almost one decade), the selection of articles that considered spontaneous pregnancies and the different sources of the articles.

IVF and ICSI have been found to increase the described complications mainly in European and United States populations; however, further research is required on the subject in Latin America.

In 2012, Pandey et al.[44] reported similar results to those of the present work, which shows that adverse effects persist despite technological advances in ART. In a meta-analysis of ART singleton pregnancies compared to spontaneous pregnancies, Qin et al.[56] identified a higher risk of hypertensive disorders of pregnancy, gestational diabetes, C-section, prematurity and very low birth weight. On the other hand,

Roque et al.[57] reported only some maternal complications (preeclampsia, placenta accreta) when comparing ART with fresh or thawed embryos.

Given that currently the *Diagnóstico de la pareja infértil y tratamiento con técnicas de baja complejidad* (Diagnosis of the infertile couple and treatment with low-complexity techniques)[58] clinical practice guidelines do not establish the risks associated with ART, it is essential to provide more attention and care to pregnancies resulting from ART.

Conclusions

Different factors during a spontaneous pregnancy can result in obstetric and perinatal complications, to which other factors are added in pregnancies achieved by ARTs such as IVF or ICSI,[59,60] which increase the risk of experiencing said complications. Couples who decide and are candidates for ART should receive complete and clear information that includes the risk factors and complications of the procedure they are to undergo, in addition to careful preconception counselling aimed at optimizing general health, identification of reproductive disorders and at the possibility for these pregnancies to be managed as high-risk pregnancies.

Finally, more prospective cohort studies are needed in order to identify which IVF and ICSI factors influence on the development of complications and how they could be minimized or prevented.

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BRIEF ARTICLE

Sexual health educational intervention in medical students

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Abstract

Introduction: *The National Autonomous University of Mexico Faculty of Medicine created the Adolescent Pregnancy Prevention Program, which is aimed at students.* **Objective:** *To determine the sexual-reproductive health profile of medical students through a diagnostic questionnaire and of those who participated in an educational intervention on sexuality (three modules).* **Method:** *First-year undergraduate students, schoolyear 2017-2018, participated. Students were considered to be trained when they took at least one module.* **Results:** *The questionnaire was answered by 1157 students, 21.9 % participated in at least one module, 43.1% had initiated sexual activity and 25 % received the educational intervention. Not having used a condom in their last intercourse was identified in 20 %, and a high prevalence of intercourse under the influence of alcohol was observed.* **Conclusions:** *It is important for specific sexuality competences to be promoted among those who will be doctors in the future.*

KEY WORDS: *Adolescent pregnancy. Educational intervention. Sexuality.*

Intervención educativa sobre salud sexual en estudiantes de medicina

Resumen

Introducción: *La Facultad de Medicina de la Universidad Nacional Autónoma de México creó el Programa de Prevención de Embarazo en Adolescentes, dirigido a estudiantes.* **Objetivo:** *Determinar el perfil de la salud sexual-reproductiva de estudiantes de medicina mediante un cuestionario diagnóstico y de quienes participaron en una intervención educativa de sexualidad (tres módulos).* **Método:** *Participaron estudiantes del primer año de la carrera, ciclo 2017-2018. Se consideró que el estudiante fue capacitado cuando cursó al menos un módulo.* **Resultados:** *Contestaron el cuestionario 1157 estudiantes, 21.9 % participó en al menos un módulo, 43.1 % había iniciado vida sexual y 25 % recibió la intervención educativa. El 20 % no usó condón en su última relación y se observó alta prevalencia de relaciones sexuales bajo el influjo de alcohol.* **Conclusiones:** *Es importante promover competencias específicas en sexualidad entre quienes serán los futuros médicos.*

PALABRAS CLAVE: *Embarazo adolescente. Intervención educativa. Sexualidad.*

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Introduction

According to the World Health Organization,[1] adolescence is "the period of life in which the individual acquires the reproductive capacity, shifts from the psychological patterns of childhood to adulthood and consolidates socioeconomic independence". With the acquisition of reproductive capacity, the possibility of conceiving an unplanned pregnancy is also acquired. Approximately 16 million adolescent females in the world are estimated to give birth every year in low and middle income countries.

In Mexico, the 2012 National Health and Nutrition Survey considers adolescents to be those subjects from 10 to 19 years of age; in our country, more than 22 million individuals are estimated to belong to this group.[2] With regard to reproductive health, 90 % of adolescents were reported to have knowledge about any contraceptive method and that condom is the most commonly used. The number of adolescents who had their first sexual encounter without protection has decreased: from 57 % (2006) to 33.4 % in females, although this is still a highly vulnerable group, not only because in the first sexual intercourse they can conceive a pregnancy, but for the reasons for not using a contraceptive method.

In the 2014 National Survey of Demographic Dynamics, 44.9 % of sexually active adolescents aged 15 to 19 were reported to have declared not having used a contraceptive method during their first sexual encounter,[3] which placed them at risk for an early pregnancy or for acquiring a sexually-transmitted infection (STI). In the 2018 report of this survey, women's level of education was also reported to be a factor that influences on reproductive behavior:[4] in the 2015-2017 triennium, the overall fertility rate of women with some degree of primary education was 2.82 children per woman, while in women with secondary and higher education it was 1.75.

In this regard, the 2015 National Strategy for the Prevention of Pregnancy in Adolescents included health policies and lines of action to combat this problem and, among its transversal axes, comprehensive sexuality education was proposed.[5] Thus, educational institutions have a social responsibility to support efforts aimed at preventing adolescent pregnancy, a situation that in Mexico represents a serious public health problem due to the various social, economic and health implications it entails.

In response to this context, the Faculty of Medicine of the National Autonomous University of Mexico created the Adolescent Pregnancy Prevention Program (PPEA – *Programa de Prevención del Embarazo en Adolescentes*), aimed at medical undergraduate adolescent students, with the purpose to increase their knowledge in various sexual and reproductive health issues through an educational intervention. A research project was developed that would allow the performance of a diagnostic study (phase I) to determine personal, family or social factors related to sexual risk practices and unplanned pregnancies in adolescent students of the Faculty. With the results, the PPEA established a collaboration with the National Institute of Perinatology and the National Center for Gender Equity and Reproductive Health in order to design the specific pedagogical contents and teaching strategies that were implemented in an educational intervention (phase II). This document presents data characterizing the profile of the students who participated in the diagnostic study and who voluntarily received the educational intervention during the 2017-2018 school year.

Method

The population participating in the PPEA was composed of first-year medical students aged 17 to 19 years. The study was approved by the Research and Ethics Commissions of the institution (registry number FM-DI-028-2017). All the students included voluntarily agreed to participate after being informed on the purpose and dynamics of the research.

Phase I. Diagnosis

A 68-question self-administered questionnaire, the reliability of which had already been assessed, was applied.[6] The explored dimensions were general information, family data (mother and father), information on sexuality and sexually-transmitted infections (STIs), knowledge about contraceptive methods and substance abuse.

Phase II. Educational intervention

Three educational modules on sexual and reproductive health were designed: correct placement of male and female condoms, prevention and risks of sexually-transmitted infections and use of hormonal contraceptives. The educational intervention was based on the pedagogical model of direct instruction, which combines the teacher's explanations and guidance with the

student's practice and feedback, in order to teach procedural concepts and skills (course-workshop).[7] The contents and teaching resources were structured based on the techniques described in the official Mexican standards and clinical practice guidelines, and were reviewed by specialists in the subject, psychologists and education experts. All materials (electronic presentations, videos, brochures, infographics) were designed with a visual code suitable for the adolescent population (image design, color palette, shape structure), in order to favor the identification and acceptance of the provided information. Some anatomical models of the female and male reproductive systems were used, as well as samples of contraceptive methods as support resources during the intervention.

The modules were taught by sexual and reproductive health trainers who collaborate in the PPEA. Each module had a duration of 90 minutes. The dissemination of the course was carried out through the institutional social networks or it was offered face-to-face, and the registration was carried out with an electronic appointment system (a maximum of 15 students per session). Knowledge was assessed in each module before and after the educational intervention, which consisted of a self-administered questionnaire with 10 closed questions of the nominal-polytomous type.[8]

Statistical analysis

Data analysis was performed with the statistical software Stata 13.0 (Stata Corp). Regarding phase I, qualitative variables were described with percentages, and quantitative variables, with means. As for phase II, the student was considered to be trained when he/she took at least one of the three modules of the educational intervention. Twenty-four variables of interest were selected from the diagnostic questionnaire in order to find differences between the students who were trained and those who did not receive the educational intervention (sociodemographic, related to their sexuality, communication with parents, use of contraceptives, substance abuse and history of STIs). The chi-square test was used for qualitative variables, and Student's t-test for independent samples was used for quantitative variables. Finally, for the pre- and post-intervention evaluation of each module of the workshop, a Shapiro-Wilk test was performed to assume score differences normal distribution; when the p-value was < 0.05, the Wilcoxon test was used, and if the p-value was > 0.05 Student's t-test for paired samples was used. Significant differences were considered to exist when the p-value for all tests was < 0.05.

Results

In total, 1157 students aged between 17 and 19 years answered the phase I questionnaire; 70.2 % (812) were females and 29.8 % (345) were males. At the time of the interview, 20.1 % (232) were 17 years old; 65 % (n = 752), 18 years; and 14.9 % (n = 173), 19 years. The percentage of mothers of students who had their first pregnancy before 20 years of age was 18.5 % (n = 214); as for the parents, 10.4 % (n = 120) had their first child before 20 years of age. Other relevant data were that 43.1% (n = 499) of the students had already initiated sexual activity and 1.1 % (13) reported having suffered any STI sometime in their lives. In addition, 12.6 % (n = 146) referred smoking; 45.1 % (n = 522), having consumed alcohol; and 8.6 % (n = 99), having used some type of drug (Table 1).

Regarding the profile characterizing the volunteer students who received the educational intervention, 21.9 % (n = 254) of total population that answered the diagnostic questionnaire participated in at least one of the three modules of the workshop. Only 21.1 % of females and 25.2 % of males participated in the modules, with no gender-attributable differences being identified. Of the entire subset of students aged 17 years, only 23.7 % joined the training, as well as 21.8 % of those aged 18 years and 22.5 % of those aged 19; no significant differences were found regarding age either. Some characteristics where statistical differences were found were the following:

- *Initiation of sexual activity* (p = 0.011): 25.8 % of those who had already initiated sexual activity at the time of the survey did enroll in at least one of the modules, in comparison with 19.6 % of those who had not initiated it.
- *Number of sexual partners within the last three months* (p = 0.039): 19.6 % of the students who had not had any sexual partner enrolled in any module in comparison with 23.1 % of those who had had two or more sexual partners and 26 % of those who had had only one.
- *Anal intercourse* (p = 0.017): 31 % of those who declared practicing it enrolled in one of the modules, in comparison with 21.3 % of those who did not practice it at the time of the survey.
- *Intercourse with people of the same gender* (p = 0.001): 53.1 % of the students who answered affirmatively enrolled in the course and 21.4 % of those who answered negatively also did enroll.
- *Talking about sexuality with friends* (p = 0.048): 23.3 % of those who declared doing so enrolled

Table 1. Profile of the students who received the educational intervention on sexual and reproductive health in at least one of the three modules that were offered

Characteristics	n	Received intervention		p
		No (%)	Yes (%)	
Gender				
Females	812	78.9	21.1	0.120
Males	345	74.8	25.2	
Age (years)				
17	232	76.3	23.7	0.829
18	752	78.2	21.8	
19	173	77.5	22.5	
Family history				
Maternal age first pregnancy				
< 20 years	214	74.3	25.7	0.185
≥ 20 years	943	78.5	21.5	
Paternal age first child				
< 20 years	120	75.8	24.2	0.604
≥ 20 years	1037	77.9	22.1	
Sexuality				
Already initiated sexual activity?				
Yes	499	74.2	25.8	**0.011***
No	658	80.4	19.6	
Age at sexual activity initiation (range)	499	16.4 (16.3-16.6)	16.3 (16.0-16.5)	0.254
Number of sexual partners (last three months)				
None	658	80.4	19.6	**0.039***
1 partner	473	74.0	26.0	
> 2	26	76.9	23.1	
Sexual activity with caressing				
Yes	658	76.6	23.4	0.300
No	499	79.2	20.8	
Oral sexual activity				
Yes	445	75.3	24.7	0.118
No	712	79.2	20.8	
Anal intercourse				
Yes	116	69.0	31.0	**0.017***
No	1041	78.7	21.3	
Intercourse with people of the same gender				
Yes	32	46.9	53.1	**< 0.001***
No	1125	78.6	21.4	
Sometime has become pregnant, even if not full-term				
Yes	10	60.0	40.0	0.177
No	1147	77.9	22.1	
Communication				
Speaks about sexuality with mother				
Yes	907	77.6	22.4	0.898
No	250	78	22	
Speaks about sexuality with father				
Yes	490	78.2	21.8	0.746
No	667	77.4	22.6	
Speaks about sexuality with friends				
Yes	992	76.7	23.3	**0.048***
No	165	83.6	16.4	
Speaks about sexuality with partner				
Yes	624	76	24	0.124
No	533	79.7	20.3	
Contraceptives				
Use of condom in last intercourse				
Yes	409	74.8	25.2	0.081
No	748	79.3	20.7	
Use of morning-after pill				
Yes	28	71.4	28.6	0.42
No	1129	77.9	22.1	

(*Continues*)

Table 1. Profile of the students who received the educational intervention on sexual and reproductive health in at least one of the three modules that were offered (*Continued*)

Characteristics	n	Received intervention		p
		No (%)	Yes (%)	
Substance abuse				
Frequency of alcohol consumption (weekly)				
At least once	154	72.7	27.3	0.111
< Once	1003	78.5	21.5	
Consumption of drugs				
Yes	30	63.3	36.7	0.055
No	1127	78.1	21.9	
Intercourse under the influence of alcohol				
Yes	93	76.3	23.7	0.743
No	1064	77.8	22.2	
Intercourse under the influence of drugs				
Yes	18	72.2	27.8	0.574
No	1139	77.8	22.2	
STI				
Have you ever been diagnosed with an STI				
Yes	13	69.2	30.8	0.461
No	1144	77.8	22.2	
Have you ever had an HIV test practiced				
Yes	49	73.5	26.5	0.467
No	1108	77.9	22.1	

STI = sexually-transmitted infection.

in one of the courses and only 16.4 % of those who said they did not talk about that subject with friends did (Table 1).

Finally, of the 254 students who were trained in at least one of the three modules, 218 chose to take module 1; 109, module 2; only 36, module 3. With the scores of the pre- and post-intervention assessments, statistical differences were found ($p < 0.05$) in all three modules (Fig. 1).

Discussion

Various national programs of sexual and reproductive health educational interventions have been documented in the national and international literature. In the study by Bennet and Assefi (2005), heterogeneity was reported in the implementation of the programs, as well as in the duration, objectives, subjects and strategies that are used. Although a change was documented in female adolescents' sexual behavior, the effects were moderate and, ultimately, possibly with a short-term impact.[9] In the present study, evidence was obtained of an increase in the knowledge of the students who received the educational intervention, and the results provided a characterization of the college population interested in attending course-workshops on sexual and reproductive health issues. The profile allowed the group of researchers in charge of the PPEA to design an ad hoc intervention for vulnerable groups that might find themselves in risk situations, such as the students who referred not having used a condom during their last intercourse.

Although the PPEA does an important work at disseminating the courses that are offered, only 20.7 % of the students who did not use a condom in their last sexual encounter attended a workshop. Females are currently the predominant population group in the Faculty of Medicine and who are exposed to higher reproductive risks, among which unplanned pregnancy is one of the most relevant.

Even when this was a population group where the prevalence of STIs is low (1.12 %), given that their average level of education is above the national mean,[10] the fact that only 30.8 % of participants with a history of STI diagnosis attended the module draws the attention. The figures are equally worrying regarding those who indicated having had an HIV test practiced (4.23 %), out of which less than one quarter were interested in any of the modules that make up the educational intervention.

We consider it relevant highlighting the prevalence of anal intercourse in a group of young people who mostly defined themselves as heterosexuals, with this practice being increasingly used and constituting a field of research that should be studied in depth. The trend that has been identified is that this practice is

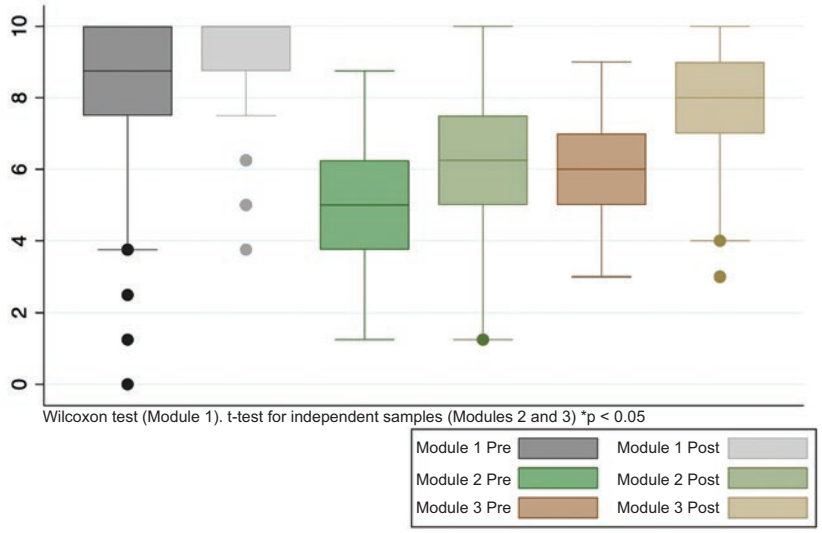

Figure 1. *Scores obtained by 254 students who were trained in at least one of the three modules of a course-workshop on reproductive health; 218 chose to take module 1; 109, module 2; 36, module 3. With the pre- and post-intervention assessment scores, statistically significant differences (p < 0.05) were found in all three modules.*

being chosen in order to avoid an early pregnancy and that the interest of this group in the intervention offered by our Program was in order to know the methods for protection against STIs.

Finally, the association between substance abuse (alcohol and drugs) and sexual intercourse among university students is documented in several investigations.[11,12] In our study, we observed that the prevalence of students who have had sexual intercourse under the influence of alcohol was 8 %, which is higher than that related to sexual activity under the influence of any drug (1.5 %); therefore, the intersection of risk behaviors with adolescents' mental health should not be overlooked, which is a situation that is also duly taken care of by the PPEA, at least to refer them to the corresponding areas.

As previously described, national and international studies have documented that adolescents who have a lower education level or a low level of academic aspirations have higher fertility rates or are at higher risk for incurring a pregnancy situation.[13,14] The educational intervention the PPEA has promoted for three years has shown positive effects on the increase of knowledge on sexual and reproductive health issues among the students who have participated, and it is therefore important to consider this strategy as part of the academic curriculum of the Faculty. This could favor the development of specific competences in the understanding of the different sexual practices, STIs, abortion, reproductive coercion and violence within the legal framework, among others.[15] In addition to the impact on personal development, the PPEA might provide an additional long-term benefit to the general population, since the educational intervention considers the minimal conceptual elements the general practitioner should possess in matters of sexual and reproductive health.

Conclusions

There is still a great deal of work to do, and although the PPEA is a young initiative, the Faculty of Medicine of the National Autonomous University of Mexico has placed its bet on empowering adolescent students with a fundamental tool for the healthy development of their sex life and for adequate decision making: knowledge.

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SYMPOSIUM

Antimicrobial resistance. Its importance and efforts to control it

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Abstract

The World Health Organization estimates that bacterial resistance will cause 10 million deaths by 2050. As part of the Global Action Plan on Antimicrobial Resistance, it proposed networks of specialized laboratories in order to preserve strains and optimize the use of antimicrobials. That is the case of the Latin American Surveillance Network of Antimicrobials Resistance. In a 2019 study, the main bacteria of the ESKAPE group (which are highly resistant to the most widely used antibiotics) that cause infections in Mexican Hospitals were identified to be multidrug-resistant (MDR) and extended-spectrum beta-lactamase (ESBL)-producing Klebsiella spp., ESBL-producing Enterobacter spp., Acinetobacter baumannii, MDR Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecium. With information on drug resistance, regimens are recommended to treat infection caused by Helicobacter pylori, a pathogen related to the development of cancer and whose prevalence in the adult population of Latin America is estimated to range between 60 and 70 %.

KEY WORDS: *National Strategy. Antimicrobial resistance. ESKAPE group. Helicobacter pylori.*

Resistencia antimicrobiana. Importancia y esfuerzos por contenerla

Resumen

La Organización Mundial de la Salud estima que en 2050 la resistencia bacteriana ocasionará 10 millones de muertes. Como parte del Plan de Acción Mundial sobre la Resistencia a los Antimicrobianos propuso redes de laboratorios especializados, para conservar cepas y optimizar el uso de los antimicrobianos. En un estudio de 2019 se identificó que las principales bacterias del grupo ESKAPE (con alta resistencia a los antibióticos más usados) que causan infecciones en hospitales de México son Klebsiella spp. resistentes a múltiples fármacos (MDR) y productoras de betalactamasa de espectro extendido (BLEE), Enterobacter spp. BLEE, Acinetobacter baumannii, Pseudomonas aeruginosa MDR, Staphylococcus aureus meticilinorresistente y Enterococcus faecium resistente a vancomicina. Con la información de resistencia a los fármacos se recomiendan esquemas para tratar la infección causada por Helicobacter pylori, relacionado con el desarrollo de cáncer y cuya prevalencia en la población adulta de Latinoamérica se estima es de entre 60 y 70 %.

PALABRAS CLAVE: *Estrategia Nacional. Resistencia antimicrobiana. Grupo ESKAPE. Helicobacter pylori.*

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Introduction

Antimicrobial resistance is defined as the ability of a microorganism to resist the effects of antibiotics; it is an inherent characteristic of bacteria or it can be an ability that is acquired during the infectious process.

According to the United Nations (UN), bacterial resistance is one of the main health threats, as it endangers global priorities such as human development. In view of the profound implications in economic activities, food supply, tourism and migration flows, based on this redefinition, cooperation, consultation and surveillance mechanisms have been established with more or less support from each country.

There are three types of infections according to the resistance of the bacteria that cause them:

- *Enterobacteriaceae* infections, due to their impact on morbidity and mortality.
- *Acinetobacter* spp. infections. Reports in several hospitals reveal that there are limited therapeutic options with available antibiotics. Antibiotics generated in recent years also have no activity against these multi-drug resistant (MDR), extensively drug resistant (XDR) or pandrug resistant (PDR) strains.
- Other serious infections, such as those caused by *Pseudomonas aeruginosa*, which can cause high mortality.

The motto of the World Health Organization (WHO) regarding resistance to antimicrobials is "no action today, no cure tomorrow", since it is estimated that bacterial resistance will cause 10 million deaths per year by 2050, and a reduction of between 2 and 5 % of gross domestic product in some countries. Based on its risk report, during the 2013 World Economic Forum, this health problem was positioned at the same level as the risk of weapons of mass destruction proliferation and global economic crisis.[1]

The 17 sustainable development goals of the UN 2030 agenda are a call to action to all countries to eradicate poverty and protect the planet, as well as to guarantee peace and prosperity; seven of these objectives have to do with antimicrobial resistance.[2]

In the 2015 Global Action Plan, the Global Surveillance System was established, where there was a resolution by the WHO assemblymen/women group on antimicrobial resistance, with the idea of presenting the countries' advances in the 72nd World Health Assembly, in May 2019; unfortunately, neither the Mexican Minister of health nor the undersecretary were able to attend in order to present the country's advances.[3]

In the Global Action Plan there are five objectives related to the strengthening of knowledge based on surveillance and research studies.

With regard to global actions, countries have different methodologies to address the problems. An exemplary case is that of the United States, a country that has joined the Global Antimicrobial Resistance Surveillance System (GLASS), which refers to the use of surveillance standards whereby improving patient safety is intended. The need to ensure data quality and standardize the reports on resistant bacteria stands out.[4]

In the United States, the Centers for Disease Control and Prevention (CDC) analyze healthcare-associated infections (HAIs) through a national network that has more than 24,000 health facilities, as well as more than 63 thousand individual users, which gives certainty about the quality of the generated data.[5]

The WHO collects and analyzes data on antimicrobial resistance and adds them to information related to the countries following standard definitions; in 2011, it dedicated World Health Day to the fight against antimicrobial resistance; in 2015, it recommended member countries to develop a national plan to fight antimicrobial resistance; in 2017, it launched the Global Antimicrobial Resistance Surveillance Program.

In 2017, the National Strategy for Action against Antimicrobial Resistance was announced in Mexico, which was published as *Action plan against antimicrobial resistance for Mexico* and whose working group includes the Ministry of Public Education, the Ministry of Health, the Ministry of Agriculture and Rural Development, the Ministry of Environment and Natural Resources, the Ministry of Economy, the Ministry of Treasury and Public Credit, the Ministry of Foreign Affairs, the Mexican Institute of Social Security and the Institute of Social Security and Services of State Workers, under the coordination of the Federal Commission for Protection against Health Risks. With this multi-sectoral strategy, epidemiological and health surveillance, the use of antimicrobials in human health and research are aligned.[6]

On June 5, 2018, an agreement was published in the Official Gazette of the Federation declaring the mandatory adherence to the National Strategy for Action against Antimicrobial Resistance by all the institutions that make up the National Health System.[7]

Bacterial resistance regional networks

Research on microbial resistance to antibiotics is conducted in interdisciplinary laboratory networks and in national, regional and international research associations. Interdisciplinary approaches are generally useful, even indispensable, for a successful investigation of complex problems such as bacterial resistance. The networks generate information regarding affected subjects, in which hospitals, to which magnitude and extent, what types of antibiotics are used, impact on mortality, severity of the disease and economic impact, among other data. The best definition is that microbial resistance surveillance networks favor better actions for prevention and control.

Latin American Network for Antimicrobial Resistance Surveillance (ReLAVRA)

The Latin American Network for Antimicrobial Resistance Surveillance (ReLAVRA – *Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos*), created in 1996 with support from the Pan American Health Organization, has the mission to obtain reliable, timely and reproducible microbiological data to be used in the improvement of patient care through the establishment of sustainable quality assurance programs.[8]

The first network in Mexico was that of the Mexican Association of Infectology and Clinical Microbiology, which operated from 1997 to 2000, and worked in a quality laboratory system for the study of gram-positive and negative bacteria. Then, the UME Hospital Network followed. In turn, the National Autonomous University of Mexico, through the University Program for Health Research, established the University Plan for the Control of Antimicrobial Resistance.[9]

The Thematic Network for Drug Resistance Research and Surveillance is perhaps the most ambitious and productive, since it includes 50 hospitals in 20 different states.[10,11]

ReLAVRA includes four countries: Argentina, Brazil, Mexico and Spain; the latter involves the participation of the University of Madrid and the *Complutense* University. This research network allows the exchange of knowledge and learning between postgraduate students and researchers.

The reduced number of networks based on specific pathologies and with indicators obtained from the comparison of community-acquired infections versus HAIs and other targets limits the construction of denominators to know the real impact of antimicrobial resistance. The WHO and the Pan American Health Organization have made an effort in the region of the Americas to define guidelines and convene member countries to work in the development of surveillance plans. The guidelines indicate basic elements for implementing and adapting surveillance networks according to the capacities and development of the region (GLASS).[4]

In Mexico, national antimicrobial resistance surveillance programs should go from being expository to being evolutionary and guarantee the quality of information, which must be public and transparent in order to adequately guide actions at the local and regional levels and be accessible to international agencies.

WHO recommendations on antimicrobial resistance in HAIs

Seven-hundred thousand cases of antimicrobial resistance have been recorded, which is more than those of cancer, cholera, diabetes and diarrhea. Due to its impact, antimicrobial resistance requires an investment of 2 to 3.5 % of gross domestic product; if this is not carried out by 2050, estimates indicate that there will be more than 10 million deaths per year.

Antimicrobial resistance can be originated by two mechanisms:

- Artificial selection due to inadequate antibiotic treatment, in which resistant clones are selected.
- Natural selection, which refers to horizontal transfer of genes, where there is an acquisition of plasmids with resistance genes, which increases the prevalence of resistant bacteria.[12]

In the United States, the CDCs point out the need to early prevent and detect bacterial resistance. Identification, control, monitoring and surveillance are the only actions that can help prevent the spread of antimicrobial resistance.

Although there are examples on how antimicrobial resistance spreads in the environment, in the community and in hospitals, it is necessary for research to delve into either of these areas, as well as to manage and know what is going on at those levels.[13]

Reports indicate that there is antimicrobial resistance to new antibiotics that are launched onto the market, with an example among many being linezolid, which started being marketed in 2000 and by 2001 there were already reports of resistance.[14]

In 2017, the WHO promoted the investigation and development of antibiotics that are no longer produced

by the pharmaceutical industry; furthermore, it pointed out that there are microorganisms with critical priorities because they cause infections with high morbidity and mortality, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterococcus*, *Helicobacter pylori*, *Salmonella*, *Campylobacter* and *Neisseria gonorrhoeae* (responsible for cephalosporin- and fluoroquinolone-resistant sexually transmitted infection); as medium priority was left *Streptococcus pneumoniae*, for which establishing its resistance profile is necessary, in addition to *Hemophilus influenzae* and *Shigella*.

One suggestion is to stratify bacteria as MDR, XDR and PDR, as it is done for *Mycobacterium tuberculosis*, since there are increasingly frequent reports of strains with these characteristics.

The WHO proposes an action plan based on raising awareness on the problem, strengthening knowledge and reducing the incidence of infections through preventive measures such as environmental sanitation, hand washing and optimal use of antimicrobials, both in humans and animals.[5] The action plan includes improving knowledge and understanding of antimicrobial resistance in local and national settings, surveillance of its incidence, optimization of the group of antibiotics and development of containment measures. Knowledge about the pharmacodynamics and pharmacokinetics of these antimicrobials, the mechanisms of action of antibiotics and antimicrobial resistance and transmission, as well as the assessment of the magnitude of prevalence depends on microbiologists and doctors.

The microbiologist can collaborate in the training of health personnel and carry out campaigns of awareness and understanding of the problem by participating in undergraduate education, as well as by strengthening knowledge through surveillance and research. In the laboratory, microbiologists can investigate the mechanisms of resistance, and detect, confirm and measure the impact of antimicrobial resistance, as well as provide microbiological knowledge, and thereby support the doctor in the development of treatment guidelines based on local epidemiological studies in human beings, animals and the environment.[15]

Information users should know the different strategies, which consist of:

- Strengthening knowledge in order to make a good use of information, both locally and nationally.
- Measuring the regional trend of antimicrobial resistance.
- Prioritizing strategies, and formulating a consensus and global recommendations.
- Determining the components of the surveillance system and the type of samples arriving to laboratories.
- Characterizing the antimicrobial sensitivity profile,[6] with internal and external protocols and quality controls.
- Submitting reports and ensuring that they are accepted and applied in hospitals or in the community, as appropriate.

Many of these measures are already regulated; for example, antibiotic sensitivity tests are carried out in laboratories according to the Clinical and Laboratory Standards Institute (CLSI), which updates its standards and guidelines on an annual basis.

There are levels of surveillance that can be prioritized and that can serve to determine which the empirical treatment should be, when to apply hospital or individual programs (if they exist) regarding the use of antibiotics and infection control.

ReLAVRA supports the WHO criteria to determine what does occur at each country of the region. In order to reduce the incidence of infections, effective hygiene and prevention and control measures are recommended, such as effective hand hygiene, cleaning procedures, reduction of healthcare-associated infections, vaccination, and environmental sanitation; regarding animal health, biosafety and hygiene and sustainable animal production are also indicated.

Regarding the above, microbiologists can collaborate with proper management and identification of clinical samples, with the development of appropriate cultures and the performance of accurate and timely sensitivity tests, with the surveillance of patients and the environment, when required. With regard to early detection of events that can turn into outbreaks in hospitals and in the community, they can collaborate with microbiological data, characterization of outbreaks, evaluation of the spread of nosocomial and community pathogens, assessment of the impact of prevention strategies (vaccines) and alerting health personnel on the emergence of antimicrobial resistance in pathogens already under surveillance or on emerging pathogens.[8]

The Network must insist on the best use of antimicrobials, on timely and adequate diagnosis and on reporting according to the place of infection, with special surveillance tests, as well as on the custody of strains.

The CLSI formulated some rapid, complementary and confirmatory tests that can help guide the doctor for evaluation or alternative treatments.

Carbapenem-resistant *enterobacteriaceae* (CRE) global spread started in North Carolina, and from there it disseminated to New York, Israel and Europe; carbapenemase-producing CREs of the New Delhi metallo-β-lactamase (NDM) type originated in India, and from there they spread to several countries.[16]

As for the animal population (fish, domestic fowl and pets), studies are needed to assess environmental resistance.[17]

In order to comply with the Global Action Plan on Antimicrobial Resistance, it is necessary to ensure the sustainability of evaluation through research, which requires investment and the establishment of procedures, as well as accepting the role of the laboratory, which will impact on patient benefit.

ESKAPE group in Mexico

Antimicrobial resistance is a worldwide public health problem related to human and non-human antimicrobials use; it is one of the subjects addressed in the multisectoral approach called 'One Health', which brings the WHO, the United Nations Food and Agriculture Organization and the World Organization for Animal Health together.[18]

Currently, the most serious infections that threaten human life are caused by a group of antibiotic-resistant bacteria, which the American Society for Infectious Diseases has named the ESKAPE group. ESKAPE is an acronym formed by the name of six bacteria that cause serious infectious diseases and whose pathogenicity and antimicrobial resistance mechanisms are evolutionarily highly developed.[19] ESKAPE group bacteria are a critical health threat because they cause a substantial percentage of HAIs in modern hospitals (the CDCs indicate that they are responsible for two thirds of HAIs), represent the majority of isolates whose resistance to antibiotics is severe and are pathogenesis, transmission and resistance paradigms, and therefore drive the doctor to therapeutic dilemmas.

The bacteria of the ESKAPE group are the following:

1. Vancomycin-resistant *enterococcus faecium* has emerged as a nosocomial pathogen that causes urinary tract, wound and bloodstream infections, and has also been linked to infections deriving from the use of catheters and surgical procedures.
2. *Staphylococcus aureus* is part of the microbiota of the skin and moist areas of the human body. In Mexican carriers, strains with variable antimicrobial susceptibility have been identified. With regard to HAIs, *S. aureus* has been associated with bacteremia, surgical wound infections, endocarditis, pyogenic arthritis, osteomyelitis, and skin and soft tissue infections. In isolates, it exhibits resistance to antibiotics and beta-lactams, including methicillin, in which case it is called MRSA (methicillin-resistant *Staphylococcus aureus*).
3. *Klebsiella pneumonae* is an enterobacterium that represents a level of urgent threat; it causes respiratory, urinary and bloodstream infections, acquired both in hospitals and in the community. In hospitals, where this pathogens can spread and cause outbreaks, extended-spectrum β-lactamase (ESBL)-producing strains have been isolated, including carbapenemase-producing strains.
4. *Acinetobacter baumannii* is currently recognized as a pathogen causative of infections in patients admitted to the intensive care unit; it causes pneumonia and bacteremia associated with the use of catheters. At present, most isolates show multidrug resistance, even to carbapenems.
5. *Pseudomonas aeruginosa* is an opportunistic nosocomial pathogen that causes pneumonia, bacteremia, urinary tract and surgical wound infections, which is also found in the environment. The number of infections caused by this bacterium has increased and it is mostly MDR.
6. *Enterobacter cloacae* is a bacillus that is present in the digestive tract. It has been associated with urinary tract and surgical wound infections and bacteremia, but more often it has been identified in hospitalized immunocompromised patients. Due to the low permeability of its outer membrane, enterobacteria exhibit resistance to penicillin, oxazoyl penicillin, clindamycin, lincomycins, glycopeptides (vancomycin and teicoplanin) and macrolides.

The first study on ESKAPE group bacteria surveillance in Mexico was published in 2012, and was conducted over the course of one year at the Intensive Care Unit of the University Hospital in Monterrey, Nuevo León. A total of 1693 pathogens from different clinical samples were analyzed; ESKAPE group bacteria were found to account for 64 % of isolates. *A. baumannii* was found to be the most common, followed by *P. aeruginosa*.[20] *P. aeruginosa* and *A. baumannii* were MDR, even to carbapenems; 20 % of *A. baumannii* isolates were PDR; 36 % of MDR *K. pneumoniae* isolates were of the extended-spectrum β-lactamase-producing type. The resulting infections had few antimicrobial treatment options. Regarding gram-positive bacteria, 62 % of *S. aureus* isolates

showed resistance to methicillin and 4 % to vancomycin; as for *Enterococcus* spp., 10 % were observed to be resistant to vancomycin.

The second work published in Mexico was carried out at the National Cancer Institute.[21] The ESKAPE group bacteria isolated from blood cultures of cancer patients were analyzed. More than 33 thousand blood cultures obtained over a 10-year period were analyzed. In 17 % of the blood cultures there was bacterial isolation, with 92 % of them being MDR and 58 % gram-negative bacilli; 6 % were *K. pneumoniae*, out of which 11 % were ESBL-producing; *P. aeruginosa* was identified in 6 %, out of which 11 % were MDR. *E. cloacae* was found with a high BLEE production percentage, as well as *A. baumannii*, with 24 % being MDR. Gram-positive pathogens showed 37 % of MDR, 9 % were *S. aureus*, 21 % were resistant to methicillin, 2 % were *Enterococcus* spp., and 32 % were resistant to vancomycin. The researchers concluded that MDR strains of the ESKAPE group were the most frequently isolated strains in patients with hematologic malignancies.[21]

The third report was published by the University Program of Health Research of the National Autonomous University of Mexico, and it shows antimicrobial resistance current status in Mexico. A total of 11,900 isolates obtained during 2016 and 2017 from 14 hospitals of six states of the Mexican Republic were included. The majority of isolates (73 %) came from urine cultures; *Escherichia coli* was identified in 91 %, and *K. pneumoniae* in 8.5 %; 27 % of isolates were obtained from blood cultures. Gram-negative bacteria were *E. coli*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa* and *A. baumannii*. *K. pneumoniae* and *E. cloacae* showed resistance to all cephalosporins and 60 % of the isolates were ESBL producers, which clearly shows the urgency of interventions to control the problem of antimicrobial resistance. The gram-positive isolates studied were *S. aureus*, which accounted for 21 %.[9]

The most recent work, in which 47 hospitals from 20 states of Mexico participated, was published in March 2019. A total of 22,943 isolates obtained from January to June 2018 were studied, with a high percentage of carbapenemase-resistant gram-negative bacteria being found: more than 50 % of *A. baumannii*, 40 % of *P. aeruginosa* and 12 % of *Klebsiella* spp. and *E. cloacae*. MDR was quite high in *A. baumannii* (53 %) and *K. pneumoniae* (22 %). In the group of gram-positive bacteria, 21 % were methicillin-resistant *S. aureus* and 21 % were vancomycin-resistant enterococci.[10]

In summary, the main bacteria of the ESKAPE group that cause nosocomial infections in Mexico were MDR ESBL-producing *Klebsiella* spp., ESBL-producing *Enterobacter* spp., MDR *A. baumannii* and *P. aeruginosa* (both resistant even to carbapenems), methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium*.

In recent years, infections by ESKAPE group bacteria have increased in Mexico, mostly in intensive care units; isolates have been characterized as MDR. MDR *A. baumannii* and MDR *K. pneumoniae* require immediate attention, as well as vancomycin-resistant MRSA and *E. faecium* strains. It is important to consider that these isolates are the starting point for outbreaks of infections related to healthcare-associated bacteremia.

Finally, it is necessary to update and maximize the use of antimicrobial treatments, in order to preserve their usefulness. Information from studies conducted in Mexico points at the urgency of implementing measures to control antimicrobial resistance. If we don't act today, there will be no cure tomorrow.

Antibiotics can prevent *Helicobacter pylori*-associated gastric cancer

Gastric cancer is the second cause of mortality due to tumors in the world. Particularly in developing countries, treatment success depends on early diagnosis; unfortunately, this cancer alerts the patient too late to seek medical help.[22]

The Global Cancer Observatory (GCO) points out areas where gastric cancer rates are higher, such as Asia and Latin America. In Mexico, approximately 2 billion pesos have been estimated to be spent in direct costs related to gastric cancer and breast cancer only during the first year of medical care. The WHO estimates that the number of patients affected by these neoplasms will double by 2020.[23]

The main risk factor for this cancer is the epsilon proteobacterium *Helicobacter pylori*, which has an extraordinary ability to colonize the stomach of patients. Although in most cases the infection is asymptomatic, in some it is the cause of peptic ulcer and, in worst case scenario, of gastric cancer. The discovery that an infection was a risk factor for cancer has led to major changes in the management of modern medicine.

H. pylori infection global prevalence remains high, although it is declining in many regions of the world; however, in Asia and Latin America, 60 to 70 % of adults have been estimated to be carriers of this pathogen.[24]

In Mexico, a seroprevalence study was carried out with more than 11 thousand sera from representative patients of all ages and from all states of the Mexican Republic. The infection was found to have its onset within the first years of life, as it occurs in developing countries, and after 20 years of age, more than 70 % of adults are infected and remain with high infection rates throughout their lives.[24]

The reconstruction of *H. pylori* natural history indicates that during childhood this pathogen colonizes the gastric mucosa, where it establishes a signaling towards the epithelium, which responds with an inflammation reaction that causes gastritis, which in most cases is chronically established and can remain asymptomatic throughout the entire life. However, there is exaggerated inflammation of the gastric mucosa that can lead to atrophy when the bacteria have virulence genes and the epithelium shows higher sensitivity to the inflammatory response. If the inflammation and the bacterium that causes it remain, pre-neoplastic lesions can develop, which will eventually evolve to gastric cancer.

Solid evidence has been identified indicating that the infection can have a beneficial effect within the first years of life: epidemiological studies show an inverse association between *H. pylori* infection and adenocarcinoma of the esophagus. Apparently, when the bacterium is in the stomach, it acts as a biological buffer that prevents reflux and constant contact with acid in the esophagus, which ultimately leads to adenocarcinoma.[25]

H. pylori infection has also been found to be associated with a reduction in the risk for asthma and allergy, which is why this relationship with other autoimmune diseases is being studied. In Germany, newborn mice models showed that dendritic cell-produced interleukin 18 stimulates and differentiates regulatory T cells that inhibit autoimmune responses. Apparently, *Helicobacter pylori* stimulates regulatory T cells in the stomach during childhood and helps to prevent autoimmune diseases. Due to the above observations, it is not certain whether *H. pylori* infection should be eradicated, since there are signs that this bacterium is part of stomach microbiota and has beneficial physiological functions; therefore, during the first years of infection there is no major harm.[26] Precancerous lesions appear after 40 years of age, and actions should be taken before they manifest themselves in order to prevent the development of gastric cancer.

Recommendations in the treatment of antimicrobial-resistant H. pylori

International recommendations are mainly based on studies carried out in Europe and China; research in the United States is scarce, and in Canada there is no reliable information on resistance of this bacterium.[27,28]

In Mexico, clinical trials have been carried out with different therapeutic regimens. Triple standard therapy was tested in several thousand patients from seven places in Latin America: Mexico (Sonora and Chiapas), Honduras, Nicaragua, Costa Rica, Colombia and Chile. In the populations where the infection was eradicated, treatment for 14 days was the most effective and showed completely different results to those observed in China and Europe. Hence the importance of regional, local and national studies, in order to know the true efficacy of treatments in different populations.[29]

Taking into account the previous research and other investigations carried out by the Latin American Network for Antimicrobial Resistance Surveillance, in the Latin American 2014 consensus, triple standard therapy for 14 days is recommended as the first option, and as the second, the combination of omeprazole, amoxicillin and clarithromycin, where clarithromycin resistance defines the treatment usefulness.[30]

In Mexico, *Helicobacter pylori* resistance to antimicrobials has been studied for approximately 20 years. When the European consensus was established, it was below 5 %, and clarithromycin-specific resistance was 12 %, although this antibiotic was still clinically useful; resistance to metrodinazole was 40 %, although with variations; in the different periods examined, 7 % resistance to amoxicillin was found. In the last collection of strains in 2017, 60 % resistance to metrodinazole was recorded, and resistance to clarithromycin was relevant.[31]

In 2018, the 4th Mexican Consensus on *Helicobacter pylori* was established in collaboration with the Mexican Association Gastroenterology, where as a first line of treatment for regions with high rates of dual resistance (clarithromycin and metronidazole), the quadruple regimen is recommended for 14 days, with the possibility of considering two options:[31]

- Quadruple therapy with bismuth salts: proton pump inhibitor, bismuth subcitrate, tetracycline and metronidazole.
- Quadruple therapy without bismuth (concomitant therapy): bismuth subcitrate, amoxicillin, clarithromycin and metronidazole.

In 2014, the WHO convened *Helicobacter pylori* experts for the development of recommendations for countries where gastric cancer is a serious problem. There is a proposal of basic screening to identify candidates for the bacterial eradication regimen,[32] indicating that high-risk populations can be detected and age groups selected in a country. For example: in Mexico, the highest mortality rates due to gastric cancer are observed in Yucatán, Chiapas, Zacatecas and Baja California, states where it would be important for attention to be focused on.

Helicobacter pylori infections continue to be common in Mexican adults; 3 % of them evolve to gastric cancer, with a high mortality rate and very high costs for the health system. Current Mexican consensus has corrected first-choice treatment regimen and eradication of the infection in adults older 40 than years without pre-neoplastic lesions is expected to be an effective measure to prevent the development of gastric cancer; however, this is something that remains to be proven.[30]

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