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ORGANIZACIÓN Y DESINCRONIZACIÓN DE LOS RITMOS CIRCADIANOS EN ENFERMERAS Y MATRONAS ITALIANAS: ACTIVIDADES SOCIALES Y LABORALES

ORGANIZATION AND DESYNCHRONIZATION OF CIRCADIAN RHYTHMS IN ITALIAN NURSING AND MIDWIFERY: SOCIAL AND WORKING ACTIVITIES

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TITULO: *ORGANIZATION AND DESYNCHRONIZATION OF CIRCADIAN RHYTHMS IN ITALIAN NURSING AND MIDWIFERY: SOCIAL AND WORKING ACTIVITIES*

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ORGANIZATION AND DESYNCHRONIZATION OF CIRCADIAN RHYTHMS IN ITALIAN NURSING AND MIDWIFERY: SOCIAL AND WORKING ACTIVITIES

Tesis Doctoral presentada en la Universidad de Córdoba

Directores:
Dr. Pablo Jesús López Soto
Dr. Fabio Fabbian

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TÍTULO DE LA TESIS: Organización y desincronización de los ritmos circadianos en enfermeras y matronas italianas: actividades sociales y laborales.

DOCTORANDA: Rosaria Cappadona

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

La doctoranda, Matrona de profesión, tiene experiencia contrastada de colaboración con grupos de investigación en Cronobiología. Enfoque que ha trasladado a su campo profesional en su trabajo de Tesis Doctoral. Experiencia que viene sustentada por amplia producción científica. En el *APPENDIX I* (*Table A: Publications*; Table B: *Conference Presentations*), del documento de la tesis, se presenta un extracto referido a los años 2019-2020.

Por todo lo expuesto, los directores de la tesis refrendan que la misma cumple los requisitos formales de calidad y originalidad, mantiene el rigor científico y académico exigible, y viene respaldada por comunicaciones científicas en congresos y publicaciones, por lo que se autoriza la presentación de la tesis doctoral.

Córdoba, 5 de febrero de 2021

Firma del director

Fdo.: Pablo Jesús López Soto

Fdo.: Fabio Fabbian

To Pippo

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Any reference contained in this document to persons of the male sex shall be understood to be made equally to persons of the female sex, and vice versa, unless the context clearly indicates otherwise.

LIST OF ABBREVIATIONS

ADI	Integrated Home Care
ANA	American Nursing Association
ACS	Acute coronary syndrome
AF	Atrial fibrillation
ASL	Local Healthcare Company
AH	Agency Hospital
APGAR	Appearance Pulse Grimace Activity and Respiration
CA	Catheter ablation
CRH	Corticotropin Realising Hormone
CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
CSI	Coronary stent implantation
DAPT	Dual antiplatelet therapy
DES	Drug eluting stents
DM	Diabetes mellitus
DOAC	Direct oral anticoagulants
DtB	Door to balloon
GERD	Nocturnal gastroesophageal reflux disease
GI	Gastrointestinal bleeding
HL	Hyperlipidemia
HAT	Hypertension
ICH	Intracerebral hemorrhage

ICM	International Confederation of Midwives
IHM	In-hospital mortality
LEA	Essential Assistence Level
LVEF	Left ventricle ejection fraction
LOS	Length of stay
M	Men
MACCE	Major adverse cardiac and cerebrovascular events
MB	Major bleeding
MI	Myocardial infarction
MOM	Median value Multiple of Median
NAA	Newer antiplatelet agents
NACE	Net adverse cardiac and cerebrovascular events
NBPC	National Birth Path Committee
NHS	National Health Service
OA	Oral anticoagulants
PCI	Percutaneous coronary intervention
RA	Repeat ablation
RLS	Restless Legs Syndrome
SSN	Service Sanitary National
TAVR	Transcatheter aortic valve replacement
TE	Thromboembolic event
TFA	Transfemoral access

TIS	Total ischemic time
TRA	Transradial access
TVD	Tricuspid valve disease
W	Women

GLOSSARY

The terms described below have been extracted from the article by Vetter (2018) entitled: "Circadian disruption: What do we actually mean?"

"Adaptation: Modification in the quality of an organism (structure or function, including behavior) enhancing its fitness."

"Amplitude: Extension of the deviation from the mean in a sinusoidal oscillation, setting the maximum (that is, peak) or minimum (that is, trough)."

"Biological clock or oscillator: A self sustained oscillator system (bridging single cells to organism) that produces rhythmic biological outputs even in the absence of external rhythmic cues, also called zeitgebers (see definition). Biological clocks exist across species in practically all phyla."

"Biological rhythm: Rhythmic output of a biological clock or oscillator (see definition)"

"Chronotype: 1) proxy for phase angle of entrainment (see definition), as for example quantified by the mid point of sleep on free days; 2) diurnal preference; and 3) sometimes subsumed under personality trait. In this review, we will only refer to 1) and 2). Used to described inter-individual differences in the phenotypic expression of circadian regulated behavioral outputs."

"Circadian rhythm: A biological rhythm with a period (see definition) of about 24 hr (derived from Latin, circa diem) that is generated by a biological clock (see definition) and that persists even in temporal isolation (i.e., in absence of all external time cues). Circadian rhythms are temperature compensated (meaning that temperature does not change the rhythm's period) and they can actively entrain (see definition)."

"Circadian system: Networks of circadian clocks within an organism. The mammalian circadian system comprises a central pacemaker (in the suprachiasmatic nucleus, SCN) and the so-called peripheral clocks in most of the cells of tissues and organs. It optimizes the daily timing of biochemical, physiological, and behavioral processes by optimizing their temporal interactions."

"Diurnal: Active during the daytime, inactive during the nighttime (e.g., humans). Opposed to nocturnal (see definition)."

"Entrainment: Active process of synchronization of an oscillator to a zeitgeber (see definition). Entrainment will result in a stable phase relationship between the oscillator and the zeitgeber."

"Jet Lag: Transient misalignment between an individual's circadian clock and the local time (e.g., the local light dark cycle at the destination of a trans meridian flight). The circadian system will gradually entrain to the local light dark cycle. In humans on average 1 day per hour time change."

"Masking: An external cue influences rhythmic biological function, but without affecting the circadian oscillator, for example enhancing (positive masking) or suppressing (negative masking) effects of environmental light. Birds in a cage are a good example: they will hop from perch to perch under the control of the circadian clock, but will immediately stop if put into darkness"

Midwife: According to the International Confederation of Midwives (ICM), "a midwife is a person who has successfully completed a midwifery education programe that is based on the ICM Essential Competencies for Basic Midwifery Practice and the framework of the ICM Global Standards for Midwifery Education and is recognized in the country where it is located; who has acquired the requisite qualifications to be registered and/or legally licensed to practice midwifery and use the title 'midwife'; and who demonstrates competency in the practice of midwifery". (International Confederation of Midwives, 2011)

"Nocturnal: Active during the nighttime, inactive during the daytime (e.g., mice). Opposed to diurnal (see definition)"

"Period: Duration of one cycle, measured as for example the time elapsed between two peaks or troughs of a rhythm"

"Phase: Timing of a cycle defined by a reference point such as its minimum or its maximum temperature, dim light melatonin onset, dawn, or dusk"

"Phase angle of entrainment: The difference between the phase (see definition) of a biological rhythm and that of a zeitgeber (see definition). See also chronotype"

"Range of entrainment: Range of zeitgeber periods (e.g., light dark cycles) that an oscillator can stably entrain to. The experimental protocol of a 'forced desynchrony' specifically uses experimental light dark cycles that are outside of the range of entrainment to distinguish investigate circadian and homeostatic regulations separately"

"Zeitgeber: A rhythmic signal that circadian clocks use to actively synchronize (entrain) with the cyclic environment (normally 24 hr). The light/dark (LD) cycle is the most important zeitgeber for circadian clock"

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RESUMEN

INTRODUCCIÓN:

Los ritmos biológicos están presentes en todos los organismos vivos. El ritmo circadiano (del latín circa *dies*), con una duración aproximada de 24 horas, es el más estudiado en seres humanos. Los ritmos biológicos se caracterizan por múltiples mecanismos moleculares que se encargan de la sincronización y adaptación del organismo a las variaciones temporales del entorno. La preferencia individual circadiana (cronotipo) representa la manifestación fenotípica, de un mecanismo tan complejo, en muchos aspectos conductuales y de la vida diaria. Ya a finales de la década de los 70 del siglo pasado, Horne y Ostberg identificaron diferencias individuales en las actitudes circadianas y definieron diferentes cronotipos mediante cuestionarios autoevaluados con una puntuación definida. La pertenencia a un cronotipo definido parece tener un impacto en las actividades cotidianas, incluido el trabajo. Por otro lado, los ritmos circadianos biológicos podrían verse interrumpidos por las actividades cotidianas que conducen a la desincronización. Se ha informado de dos tipos principales de desincronización: rápida (jet lag) y lenta (trabajo por turnos). Recientemente, también se ha identificado el cambio debido al horario de verano o *Daylight Saving Time* (DST) como una condición desincronizante con posible impacto negativo en la salud. Por tanto, la hipótesis de partida de la presente tesis doctoral es que las actividades sociales y laborales y el cronotipo pueden estar estrechamente relacionados, y la desincronización, por ejemplo, el trabajo por turnos y el horario de verano, debe tenerse en cuenta en las matronas italianas.

OBJETIVOS:

General:

Determinar el efecto del cronotipo y la desincronización de los ritmos circadianos (trabajo por turnos y DST) sobre las actividades sociales y laborales de las matronas italianas.

Específicos:

- Evaluar las preferencias circadianas individuales, los efectos sobre el sueño y la calidad de vida percibida por las parteras.
- Determinar el efecto del cronotipo en las actividades sociales y laborales.
- Evaluar la asociación entre DST y la actividad laboral.
- Determinar el efecto del trabajo por turnos y DST en las actividades sociolaborales.

MATERIAL Y MÉTODOS:

Se emplearon dos enfoques:

a) Estudio observacional empleando cuestionarios validados a través de redes sociales, durante el año 2019. Los sujetos de estudios fueron matronas colegiadas en la *Italian Board of Nursing and Midwifery.* Las variables estudiadas fueron la preferencia circadiana individual, así como datos

laborales (turno de trabajo, experiencia laboral, presencia de errores de medicación) y sociodemográficos (edad, nivel de estudios, sexo). Se llevó a cabo un análisis por clúster para conocer la asociación entre variables.

b) Estudio caso-control retrospectivo empleando bases de datos administrativas, concretamente los certificados de asistencia al parto generados durante el período 2016-2018 en la Región de Emilia-Romagna, Italia. Se analizó el número de partos espontáneos 2 semanas antes (control) y después del DST (casos). También se analizaron otras variables secundarias como la edad gestacional, tipo de parto, tiempo de parto, peso del recién nacido, test de Apgar a los 5 minutos del parto y el uso de analgesia durante el parto. Se llevó a cabo un análisis univariante y multivariante (análisis de regresión logística).

RESULTADOS:

En la primera parte del trabajo, participaron 401 matronas (98,8% mujeres), con una edad media de 38,5±10,1 años y siendo los cronotipos más comunes los intermedios (50.3 %) y moderadamente matutinos (39%). El 48.1% de los casos auto-percibían que habían tenido "al menos una vez" riesgo de error de medicación. La percepción de riesgo de error de medicación se asoció con profesionales con una edad entre 31-35 años, que trabajaban a turnos, con una experiencia laboral entre 6-10 años, y un cronotipo intermedio.

Por otra parte, en el segundo enfoque, se evaluaron 7415 partos espontáneos, siendo la edad media de las mujeres de 31,4±10,1 años, con una edad gestacinal de 39,3±1,4 semanas y siendo el 64,7% italianas. No se encontraron diferencias significativas entre el número de partos antes y después del DST. No hubo diferencias sgnificativas para el modo de parto, edad gestacional y el número de partos espontáneos. El tiempo gestacional, peso del recién nacido, test de Apgar a os 5 minutos del parto y uso de analgesia tampoco mostraron una significación estadística. La única variable que se asociaba independientemente con el parto durante las dos semanas posteriores al DST fue la edad de la madre.

CONCLUSIONES:

El cronotipo y el trabajo a turnos en las matronas italianas influyen en el ámbito laboral, concretamente en la percepción de riesgo de error de medicación. Las matronas más jóvenes, con menor experiencia laboral, que realizan trabajo por turnos y pertenecen a un cronotipo intermedio, parecen tener un mayor riesgo potencial de error de medicación. Las horas de la mañana parecen representar el período de mayor riesgo para las trabajadoras de la salud y el trabajo por turnos no siempre está alineado con la preferencia circadiana individual. Por tanto, algunas aplicaciones

prácticas sugeridas podrían incluir, por ejemplo, la evaluación del cronotipo individual y patrón del sueño en el personal sanitario, programas de formación específicos y estrategias de intervención, como las siestas programadas durante los turnos de noche.
En cuanto a la posible alteración del ritmo operada por DST, no se encontraron diferencias en el número de partos en las semanas posteriores al cambio de hora. Este hallazgo está de acuerdo con datos anteriores obtenidos en condiciones bastante diferentes de latitud, clima y exposición a la luz. Es posible que la etiología multihormonal del trabajo de parto pueda explicar este fenómeno. Otros estudios extendidos a diferentes latitudes y etnias podrían ser útiles para la generalización de los hallazgos encontrados.

PALABRAS CLAVE: Cronobiología; Cronotipo; Turno de trabajo; Matrona; Desincronización de ritmos; Riesgo de errores de medicación; Daylight Saving Time; Enfermería; Obstetricia.

ABSTRACT

INTRODUCTION:

Biological rhythms are present in all living organisms. The circadian rhythm (from the latin circa dies), with a duration of approximately 24 hours, is the most commonly studied in human beings. Biological rhythms are characterized by multiple molecular mechanisms aiming at synchronization and adaptation of organism to the temporal variations of environment. The circadian individual preference (chronotype) represents the phenotypic manifestation of such a complex mechanism, in many behavioral and daily living aspects. As far the late 70's of the last century, Horne and Ostberg identified individual differences in circadian attitudes and defined different chronotypes by means of a self-assessed questionnaires with a defined score. Belonging to a defined chronotype seems to have an impact on everydays activities including working. On the other hand, the biological circadian rhythms could be disrupted by everydays activities leading to desynchronization. It has been reported two main types of desynchronization: fast (jet lag) and slow (shift work). Recently, also tlso the change due to Daylight Saving Time (DST) has been identified as a desynchronizing condition with possible negative impact on health. Thus, the starting hypothesis of this doctoral thesis is that social and working activities and chronotype may be closely related, and desynchronization, eg, shift work and DST, should be taken into consideration in Italian midwives.

OBJECTIVES:

General

To determine the effect of chronotype and desynchronization of circadian rhythms (shift work and DST) on social and working activities in Italian midwives.

Specific

- To assess individual circadian preferences, effects on sleep, and quality of life perceived by midwives.

- To determine the effect of the chronotype on social and working activities.

- To evaluate the association between the biannual DST and labor activity.

- To determine the effect of shift work and the time change on social and work activities.

MATERIAL AND METHODS:

Two approaches were used:

a) Observational study: by the use of validated questionnaires administered through social networks, registered midwives belonging to the Italian Board of Nursing of Midwifery were

investigated during 2019. The variables evaluated were individual circadian preference, work shift, working experience, fear of medication errors and sociodemographic, such as age and educational level. A cluster analysis was carried out to know the association between variables.

b) Retrospective case-control study using administrative databases: the certificates of attendance at birth generated during the period 2016-2018 in the Region of Emilia-Romagna of Italy were considered. The number of spontaneous deliveries two weeks before (control) and after DST (cases) were analyzed. Further variables, such as gestational age, type of delivery, delivery time, newborn's weight, Apgar test 5 minutes after delivery, and the use of analgesia during delivery, were evaluated. Univariate and multivariate analyses (logistic regression analysis) were carried out.

RESULTS:

In the first part of the work, 401 midwives (98.8% women) were enrolled. The mean age was 38.5±10.1 years and the most common chronotypes were intermediate (50.3%) and moderately morning (39%). Nearly fifty percent of cases self-perceived risk of medication error "at least once". Perception of risk of medication error was associated with midwifes aged between 31-35 years, undergoing shift work, with a working experience between 6-10 years, and having an intermediate chronotype.

In the second study, 7415 spontaneous deliveries were evaluated, the mean age of the women was 31.4 ± 10.1 years, and gestational age 39.3 ± 1.4 weeks. No significant differences were found between the number of deliveries before and after DST. There were no significant differences for the mode of delivery, gestational age and the number of spontaneous deliveries. Gestational time, newborn weight, Apgar test 5 minutes after delivery, and use of analgesia did not show statistical significance as well. Mother's age was the only variable found to be independently associated with delivery during the two weeks after DST.

CONCLUSIONS

The chronotype and shift work in Italian midwives influence professional self-perception, specifically the perception of risk of medication error. Younger midwives, with lower working experience, engaged in shift work and belonging to an Intermediate chronotype, seem to be at higher risk of potential medication error. Morning hours seem to represent highest risk frame for female healthcare workers and shift work is not always aligned with individual circadian preference. Thus, some suggested practical applications could include, for example, assessment of individual chronotype and sleep attitude in healthcare personnel, specific training programs, and intervention strategies, such as time-scheduled naps during night-shifts.

As for the potential rhythm disruption operated by DST, the present study did not find any differences in the number of deliveries in the weeks following time shifts. This finding is in agreement with previous data obtained at quite different conditions of latitude, climate, and light exposure. It is possible that the multihormonal etiology of labor may explain this phenomenon. Further studies extended to different latitudes and ethnicities, could be very useful to verify the possibility of a generalization.

KEYWORDS: Chronobiology; Chronotype; Work shift; Rhythm desynchronization; Risk of medication errors; Daylight Saving Time; Midwifes.

VII. CONTEXTUAL FRAMEWORK

1. NURSING METAPARADIGM IN OBSTETRIC CARE

As a demonstration of the breadth of the very field that the discipline deals with, reference is made to the so-called **metaparadigm of nursing**, which ethymologically means "beyond the model", and therefore contains everything that is relevant to nursing *care*.

The American Nursing Association (ANA), around 1985, defined nursing differently from Virginia Henderson (which reasoned in England 30 years earlier): she said that the paradigm of nurses is to understand the patient's human responses to his illness, to make a judgment of these (nursing diagnoses) and decide on the resulting nursing treatments. At this time nursing diagnoses were born helping to complete the overall picture of the clinical method used by nurses in clinical practice.

Between these two polarities, Fawcett (1984), asserted his point of view, reporting that there are four concepts that unite nurses around the world, regardless of where they come from:

1. **the concept of person:** he is the recipient of nursing care. The person seen in his component, physical, spiritual, psychological and socio-cultural. A living system formed by the biological, psychological and social components in continuous interaction with each other and with the surrounding environment; the person interacts with the environment through the performance of life activities for the promotion, maintenance and recovery of health.
2. **the concept of disease/health relevance**: it refers to the factors that can act on the person both internally and externally. Health is therefore the ability of the person to maintain in a harmonious relationship the fluctuation of processes with the needs of the organism in relation to the context.

   Health as a state of perfect coherence of all parties, interdependent, a state of harmony, since the modification of one part, involves the modification of another part or the whole system.

3. **the concept of nursing:** it describes what it is, what nurses do, what the role of the nurse is and her interactions with people. So it defines their contribution to patients. It aims to facilitate interaction between the person and the environment in carrying out life activities for the promotion, maintenance and recovery of health, replacing the person when the interaction is missing, helping the person when interaction is poor, or informing the person when the interaction is inadequate.
4. **the concept of environment:** it refers to the factors that can act on the person both internally and externally. The set of all the conditions, circumstances and influences that surround people and act on their behavior.

The 50aesarean50er of nursing therefore represents an interest in the whole of the human being and his needs, in the way in which the individual lives his health and his disease, for the one with which he takes care of himself during the disease and for the one with which he asks for and receives nursing care while maintaining the continuous interaction of man with the environment in which he is living.

2. ITALIAN NATIONAL HEALTH SISTEM

According to the Constitution of the Italian Republic (1947) there are two fundamental articles that constitute the welfare of the country.

Article 32 declare the right to health care and Article 38 enshrines the right to social assistance for persons who are disabled and deprived of resources, while also legitimizing private care.

Law No 833 of 23 December 1978 is the final regulatory point of a work of great change for Italian health. This law is based on two innovative concepts: the universality of the right to health and the unity/globality of the person's need.

The establishment of the National Health Service **(NHS)** has three essential features:

1. to be a universal system, covering the whole population;
2. be a unified system because a single contribution covers all risks;
3. be a uniform syste, as it guarantees the same performance to all concerned.

The change in the institutional set-up has been characterized mainly by two phenomena:

- The **regionalization** of the National Health Service through the creation of Regional Health Services (SSR)
- **The companyization,** through the transformation of the and USL into ASL (Local Health Companies) and of hospital facilities of national importance and specialized in hospital companies (AO) after verification of some requirements (Article 4 legislative decree 502/ 92).

Legislative Decree 502/1992 introduces LEAs (Essential Levels of Care) or all the services that the National Health Service is required to provide to all citizens free of charge or with participation in expenditure.

The regions have been given extensive powers in the field, not only of planning and coordinating resources, but above all of defining health policies, designing the organizational model of reference and legislative power. Legislative Decree n. 229/99 provides for which health services are guaranteed to all citizens, uniformly on the national territory. The Essential Levels of Care (LEAs) make clear the health services that all citizens have the right to receive throughout the national territory; these are relevant, effective, appropriate, affordable benefits with equal conditions.

- District assistance – includes the health and social health activities and services widespread throughout the territory, from basic medicine to pharmaceutical assistance, from specialist and outpatient diagnostics to the provision of prostheses to the disabled, from home services to the elderly and the seriously ill to territorial services (family consultors, mental health services, rehabilitation services for the disabled) to semi-residential and residential facilities (residences for the elderly and the disabled, day centers, family homes and therapeutic communities)
- Hospital care – must include all services in first aid, ordinary hospitalization, day-hospital and day-surgery, long-term care and rehabilitation facilities and so on.

2.1. The Birth path

In Italy, the Ministry of Health, with the establishment of the National Birth Path Committee (NBPC) on April 12, 2011, ensures the function of coordination between central and peripheral institutions according to the quality and safety of the birth path, as provided for in the State Regions Agreement of 16 December 2010.

Independent care by midwives of low-risk pregnancy is regulated by the Ministry of Health in 2017 with the " Guidelines for the definition and organization of independent *care by midwives to midwifery low risk pregnancies (BRO)*". These guidelines are based on the State Regions agreement of 2010 and promote organizational-welfare models in which both childbirth and pregnancy are managed independently by obstetrician staff.[1]

Two obstetric organizational models were identified in the document:

- Autonomous management in the physiological birth path (BRO) within the UO of Obstetrics Gynecology on the basis of shared risk definition protocols and grids. This model is present in Italy in at least 40 birth points, where pregnant women can choose the exclusive care of midwives;

[1] Ministry of Health, Guidelines for the definition and organization of independent care by midwives to midwifery low-risk pregnancies (BRO), 2017.

- Functional areas in the physiological birth path (BRO) in the UO of Obstetrics and Gynecology with physical separation, but adjacent or directly connected to it. These areas are referred to as *"alongside*" and are rare in Italy. Several hospitals already exist as a representative of this model.

Location of BRO functional areas: they must be located within hospital facilities home to PN and UU. OO. Pediatrics/neonatology, although not necessarily in continuity or contiguity with UU. OO. Obstetrics; this, in order to ensure, in case of relief of conditions that deviate from physiological trends or emergency/emergency situations, the rapid transfer of the birth or newborn to the areas dedicated to the management of such situations;

Territorial-hospital care paths: preparation of specific care paths for the identification of an appropriate and complete taking care of pregnancy by the territory. In this regard, it is recommended a strong link between the management of bro pregnancy in the territory and the taking charge of the woman by the midwife in *the BRO functional area* or bro autonomous *management* within the UU. OO. Obstetrics and gynecology. Counsellors and other territorial structures, as well as general practitioners and freelance gynecologists, contribute to the establishment of the integrated network of assistance to pregnant women.

The guidelines also define the standards and requirements for the creation of such organizational-welfare models. In particular, the indications that underline the importance of hospital-territory care pathways, the continuous revaluation of risk with specific classifications and obstetric competence are important. In fact, these elements are also fundamental in the management of low-risk pregnancy and represent the basis for the creation and dissemination of welfare models of this type.

Finally, in order to ensure adequate care for low-risk pregnancies, the new LEAs were approved in 2017.

3. MIDWIFE SERVICE PORTFOLIO

The World Health Organization (WHO) has been involved in drawing up recommendations concerning the regulation of the midwifery profession and its protection. In this sense, WHO documents direct states to set up their own professional regulatory system and to use bodies that protect skills and professional practice such as supervisors.

Depending on the socio-cultural "status" of the profession, each State has oriented the regulation of both the registration system and the training system. The WHO stresses the importance of the participation of midwives in systems such as professional associations that regulate the profession.

The main functions of a professional regulatory system are to bring order and control a profession, to protect the public through:

• definition and maintenance of standards for access to the profession

• maintaining a public register of all persons eligible to practice

• control and treatment of professional guilt through well-defined processes.

The importance of a body that deals with the definition of control and compliance with professional standards by equipping itself with qualified personnel to supervise the practice, ensuring its appropriate application (with the right to suspend a midwife from practice in case of illegal conduct), is a fundamental strength and protection for the profession and users.

3.1. The International Confederation of Midiwfes (ICM)

The International Confederation of Midwives (ICM) is an accredited non-governmental organization that supports, represents and works to strengthen professional associations of midwives around the world. ICM directs its activities with the aim of achieving common goals in the *care* of the mother-child dyad, that of the female reproductive sphere and the family and supports the education *and empowerment* of women and midwives, through education. ICM's mission is to ensure that all women, regardless of their economic condition, have access to midwifery care, a key factor in achieving maternal and infant mortality reduction

ICM is organized according to 4 continents: Africa, Americas, Asia-Pacific and Europe.

ICM works with many other international organizations, including the WHO and other UN agencies, global professional health organisations, including the International Federation of Gynecology and Obstetrics (FIGO), the International Paediatric Association (IPA), the International Council of Nurses (ICN), non-governmental organisations and civil society groups, to strengthen the role of midwifery globally and achieve the goals of:

- promote and strengthen the midwifery profession
- promote the objectives of the International Confederation
- work to improve women's health globally

Through some fundamental documents ICM defines the midwife, her role, her skills, educational standards of midwifery training in the world.

The document "Global Standards for Midwifery Education" (2010 modified 2013)" which defines the global ICM *standards* for midwifery *education (2010)* is certainly crucial, and aims to strengthen obstetric standards around the world by preparing fully qualified staff to provide *high quality, evidence-based health services* for women, infants and families. The pillars of ICM include an updated core of expertise for basic midwifery practice, midwifery education, midwifery regulation, and obstetrics associations.

Other documents contributing to the definition of the midwifery's profile of competence are:

- ICM Global Standards for Midwifery Education 2010; amended 2013 Companion Guidelines

- International Confederation of Midwives Global Standards for Midwifery Regulation (2011)

The founding values and principles on which ICM standards have developed recognize:

- Regulation is a mechanism by which the social contract between the obstetric profession and society is expressed
- Every woman has the right to receive treatment during childbirth by a competent midwife authorized to practise.
- Midwives are self-employed professionals; that is, they are responsible for their clinical decision-making.
- The boundaries of the scope of midwifery autonomy and collaboration with other professionals must be respected.
- Obstetrics is an autonomous discipline, separate and distinct from nursing and medical.
- Obstetrics practice is exclusive and incompatible with others.

Global standards for midwifery training worldwide provide the basis for the preparation of a midwife, and also help define expectations for the performance (skills) needed to promote the health of women and families. These minimum training standards can be broadened to include higher expectations and reflect country-specific needs.

3.2. Midwifery in Italy

The training of midwives in Italy has been in compliance with international and European standards for many years, regulated by Directive 2005/36/EC, which provides for the full autonomy of midwives for the diagnosis and assistance to pregnancy, assistance to labour, childbirth and low-risk childbirth, including the care of the newborn, under its own responsibility. It also recognizes autonomy in identifying the risk and possible complications that require medical care. In Italy,

however, the European Directive was implemented in 2007 by the Legislative Decree 206. The Decree incorporates that in the Article 48: "the midwife can carry out the assessment and surveillance of pregnancy diagnosed normal by a doctor, can prescribe and carry out examinations to evaluate the evolution of pregnancy and classify its risk and can give information to the pregnant woman about hygiene and nutrition".
This decree was then amended in 2015 by a further decree, according to which, in Article 37, it is no longer necessary for pregnancy to be diagnosed as normal by a person qualified for the medical profession.

In Italy, in 2010, the agreement between State and Regions reaffirms the importance of hospital integration and the role of family counseling in ensuring continuity of care, safety and appropriateness of care and empowerment of women. The family counselor, with this in mind, takes care of the pregnant woman, defining the level of risk of pregnancy.

In Italy, path-birth assistance as an expression of a normal and physiological process and the integration of care paths between hospital and territory has been present in national policies for many years. The need to bring birth back into a paradigm of normality and physiology and the need to offer accompanying and assistance services based on evidence of efficacy have led to the production of specific guidelines on assistance to physiological pregnancy and caesarean section. The guidelines recommend that women with physiological pregnancy be offered the care model "based on care by the midwife." In collaboration with the midwife, the general practitioner, counsellors and other territorial structures constitute the integrated care network for pregnant women. This model involves, in the presence of complications, the involvement of doctors specialized in obstetrics and other specialists.

The surveys carried out by the "Istituto Superiore di Sanità" show greater access to midwifery practice delivered according to the recommendations, in the Central and Northern Regions; these include physiological pregnancy followed by midwife or family counselor, participation in birth accompaniment courses, information offer in pregnancy on breastfeeding, skin-to-skin contact after birth and rooming in, the offer of home visits in puerperium by the birth point or family counselor and the offer of information on contraception [Lauria 2012].

In contrast to the medicalization of childbirth and the use of caesarean section with percentages much higher than other countries of the socio-economic scope of Italy, it is widely demonstrated that the intervention of the midwife, even only in the courses accompanying birth, reduces the rates of caesarean section [Grandolfo 2002].

Independent midwives care of low-risk pregnancy is regulated by the Ministry of Health in 2017 with the " Guidelines for the definition and organization of independent *care by midwives to midwifery low risk pregnancies (BRO)*". These guidelines are based on a Decree (State Regions agreement 12/16/2010) and promote organizational-welfare models in which both childbirth and pregnancy are managed independently by obstetrician staff [Ministry of Health 2017].

Two obstetric organizational models were identified in the document:

- Autonomous management in the physiological birth path within the UO of Obstetrics Gynecology on the basis of shared risk definition protocols and grids. This model is present in Italy in at least 40 birth points, where pregnant women can choose the exclusive care of midwives;
- Functional areas in the physiological birth path in the UO of Obstetrics and Gynecology with physical separation, but adjacent or directly connected to it. These areas are referred to as *" alongside*" and are rare in Italy. Several hospitals already exist as a representative of this model.

The guidelines also define the standards and requirements for the creation of such organizational-welfare models. In particular, the indications that underline the importance of hospital-territory care pathways, the continuous revaluation of risk with specific classifications and obstetric competence are important. In fact, these elements are also fundamental in the management of low-risk pregnancy and represent the basis for the creation and dissemination of welfare models of this type.

Finally, in order to ensure adequate care for low-risk pregnancies, the new essential levels of care were approved in 2017.

The recognition in Italy of the midwifery profession as a health profession with its own autonomy (Law 42/99) took place with some legislative reforms:

- Legislative Decree 502/92 defined "Non-managerial professional figures operating in the social and health area with high health integration, to be trained with university degree courses [..]"; the importance of vocational training through continuing training is recognized.

- DM 740/1994 defined the professional profile of the midwife, i.e. the areas within which the midwife can practice the profession with competence and autonomy (after obtaining the enabling qualification).

- Law 42/1999 "Provisions on health professions" abolished the term "auxiliary health profession" and replaced this definition with that of "health profession", determining that the field of activity and responsibility of the health professions is defined by the professional

profiles and educational systems of the respective university degree and post-basic training courses as well as specific codes of ethics.

This Law recognizes the three fundamental rights of an intellectual profession:1. Decision-making autonomy, 2. Cultural and operational independence, 3. Professional responsibility.

- Legislative Decree 229/1999 added Article 16-ter 111 on the establishment of the National Commission for Continuing Training, which provides as members representatives of the National Federations of Professional Associations including that of Midwives, and in paragraph 4 it has given autonomy to the regions in planning continuing training in compliance with national objectives and needs at local level.

- Law 251/00 is the real framework law of the sector: "Discipline of the nursing health professions, technical, rehabilitation, prevention and the profession of midwife" which regulates the profession of nurse and midwife in this regard: "1. Operators in the health professions of the nursing sciences and the obstetric health profession carry out activities with professional autonomy aimed at the prevention, care and protection of individual and collective health, performing the functions identified by the founding rules of the relevant professional profiles as well as by the specific codes of ethics and using planning methodologies for the objectives of care.

- Law 43/2006 "Provisions on nursing health professions, obstetrics, rehabilitation, health and prevention techniques and delegation to the government for the establishment of the relevant Professional Associations" defines the exercise of the profession subject to the achievement of the university degree, issued following a final examination (degree exam that has the value of a state exam), with an enabling value for the exercise of the profession and registration in the compulsory professional register also for public employees, also subject to the achievement of the qualification. It also establishes the orders of the health professions, delegating the government to adopt one or more legislative decrees for their establishment, and defines the transformation of colleges into orders. Finally, it defines the articulation of graduate staff belonging to the health professions (professionals with the degree and university degree obtained before the activation of the degree or diploma courses, coordinating professionals holding the first level master's degree in management, specialist professionals holding the master's degree for specialist functions, executive professionals with a master's degree) and establishing the coordination function for the same staff, declining criteria and methods for the activation of this function in health organizations (the coordination function can be exercised for

professionals with first-level masters or at least three years of experience in the membership profile).

3.3. The Professional Order

Once the "enabling" degree has been obtained, the midwife, recognized as an intellectual profession has the obligation to enroll in the professional Regulator of competence (where she resides or where she exercises); failure to register prohibits the exercise of the profession that becomes ipso facto abusive (art. 348 C.P.). The member is obliged to comply with the Code of Ethics.

The National Federation of Professional Orders of Midwives (FNOPO) is a non-economic public body, the national Regulator whose purpose is the pursuit of the public interest coordinated with the particular interest of midwives.

In fact, the Orders and the Federation in guaranteeing citizens the legitimate exercise of the profession of professionals registered in the register, carry out ethical and disciplinary surveillance functions, also protect the prerogatives, independence and decorum of the profession and assume the role of representation of the same at local level (provincial/interprovincial orders) and national (Federation).

4. MIDWIFE ASSESSMENT OF OBSTETRIC HEALTH

According to the essential competencies for midwifery practice established by ICM, four groups are considered: general competencies, pre-pregnancy and antenatal, care during labour and birth, and ongoing care of women and newborns [ICM, 2019].

Regarding to general competencies, ICM state the following: "a) assume responsibility for own decisions and actions as an autonomous practitioner; b) assume responsibility for self-care and self-development as a midwife; c) appropriately delegate aspects of care and provide supervision; d) use research to inform practice; e) uphold fundamental human rights of individuals when providing midwifery care; f) adhere to jurisdictional laws, regulatory requirements, and codes of conduct for midwifery practice; g) facilitate women to make individual choices about care; h) demonstrate effective interpersonal communication with women and families, health care teams, and community groups; i) facilitate normal birth processes in institutional and community settings, including women's homes; j) assess the health status, screen for health risks, and promote general health and well-being of women and infants; k) prevent and treat common health problems related to

reproduction and early life; l) recognise conditions outside midwifery scope of practice and refer appropriately; and m) care for women who experience physical and sexual violence and abuse".

On the other hand, related to pre-pregnancy and antenatal, compentencies are: "a) provide pre-pregnancy care; b) determine health status of woman; c) assess fetal well-being; d) monitor the progression of pregnancy; e) promote and support health behaviours that improve well being; f) provide anticipatory guidance related to pregnancy, birth, breastfeeding, parenthood, and change in the family; g) detect, stabilise, manage, and refer women with complicated pregnancies; h) assist the woman and her family to plan for an appropriate place of birth; i) provide care to women with unintended or mistimed pregnancy".

With respect to care during labour and births, competencies are: "a) promote physiologic labour and birth: b) manage a safe spontaneous vaginal birth; prevent, detect and stabilise complications; c) provide care of the newborn immediately after birth."

And finally, regarding to ongoing care of women and newborns, competencies are: "a) provide postnatal care for the healthy woman; b) provide care to healthy newborn infant; c) promote and support breastfeeding; d) detect, treat, and stabilise postnatal complications in woman and refer as necessary; e) detect, stabilise, and manage; and f) provide family planning services".

II. STATE OF ART

5. CIRCADIAN RHYTHMS AND THEIR ORGANIZATION

Chronobiology is a biomedical discipline focused to the biological rhythms. Biological rhythms exist in any living organisms and, according to their period length, may be classified into: a) circadian (period of ~ 24 hours, the most studied), b) ultradian (period < 24 hours), c) infradian (period > 24 hours). Circadian rhythms are driven by circadian clocks, a machinery provided with a complex transcriptionally molecular mechanism, with an endogenous free-running period a little bit longer than 24 hours. The principal circadian clock (master clock), is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and is entrained by the light/dark alternance. Moreover, many other peripheral circadian clocks have been identified within almost all organs and tissues. The principal role of cellular biological clocks is called 'anticipation', in other words meaning that circadian rhythms help the organism to adapt to any changes or needs in an anticipatory manner,

Circadian organization extends into the physiology and behavior of multicellular organisms. Three structures, along with multiple interconnections, give raise to a central "circadian axis" common to all vertebrates, even the most primitive ones; the retina, the pineal complex, and the suprachiasmatic nucleus (SCN) of the hypothalamus (Menaker et al. 1997). The SCN coordinates the central circadian oscillator, which in turn organizes the peripheral clocks, aligning the entire circadian system to the external light/dark cycle (Tahara et al. 2018). Melatonin and cortisol are the most widely used biological phase markers to examine circadian rhythm (Klerman et al. 2002; Hofstra et al. 2008). They are secreted in a highly rhythmic manner, with the former showing maximal level in the middle of night and gradual decline towards dawn while the latter raising in the second half of the night towards early morning (Zisapel et al. 2005; Shimada et al. 2016). Both melatonin and cortisol play a role in synchronizing the circadian rhythms in peripheral tissues to the 24-h pattern and provide feedback to the SCN (Casper et al. 2014).

6. DESYNCHRONIZATION OF BIOLOGICAL CLOCKS

The circadian system (with its pacemaker in the suprachiasmatic nucleus, SCN) optimizes the daily timing of biochemical, physiological, and behavioral processes (Albrecht et al. 2012). The SCN also coordinates peripheral circadian clocks in different tissues and organs. Interference on the circadian system with environmental and/or genetic manipulations is associated with endocrine disruption (Bedrosian, Fonken, & Nelson, 2016), mental disorders (Barnard & Nolan, 2008), metabolic syndrome (Parsons et al. 2015; Roenneberg et al. 2012), neuropsychiatric disorders (Musiek & Holtzman, 2016), and cardiovascular deficits (Portaluppi et al. 2012). These consequences could, at least in part, due to circadian disruption, including misalignment between

environmental rhythm and the endogenous circadian rhythms, or misalignment or uncoupling between the different components of the circadian system (Feng et al. 2011; Martino et al. 2007).

Modern lifestyles deprive us of natural zeitgebers. Most of our time is spent indoors, daytime light exposure is drastically reduced, and experiencing artificial light increased at night, with the final result of a weakened light/dark signal. Circadian clocks have to be entrained with their 24-hr environment, because the intrinsic circadian period is on average slightly longer than 24 (Czeisler et al. 1999). The light/dark cycle is considered the most important zeitgeber for the human circadian system (Duffy & Wright, 2005), and depending on an individual's endogenous circadian period and their light environment, synchronization to the 24 hr light/dark cycle can occur within a range of different phases of entrainment. This variability in phase of entrainment can also be approximated by inter individual differences in sleep timing (Roenneberg 2007a; Fischer et al. 2017).

Electricity and consequent constant accessibility to light, energy, and food, as well as 24/7 work schedules and travel across time zones have created a quite different environment compared with only two centuries ago. On one hand, technological and lifestyle changes have positive effects on daily life; on the other, continuous light accessibility may contribute to the increasing prevalence of lifestyle diseases, such as metabolic disorders, sleep disturbances, and psychiatric illnesses (Anothaisintawee et al. 2016; Broussard & Van Cauter, 2016; Potter et al. 2016). In 1965, Aschoff, used the term desynchronization to describe the relationship between rhythms in core body temperature and sleep/wake, with periods of 24.7 and 32.6 hr. Circadian misalignment (Baron & Reid, 2014), circadian desynchrony (Sack & Lewy, 1997), and desynchronization (Aschoff et al. 1965) are widely used terms that can be considered specific types of circadian disruption, each of them potentially occurring at different levels, eg, cellular, tissutal, and organismal. The terms desynchrony and desynchronization are used interchangeably to refer to differing periods between two (or more) rhythms, whereas misalignment describes an abnormal phase angle between two (or more) rhythms. The two rhythms may be internal, or even associations of internal and external (e.g., central vs. light/dark or peripheral vs. feeding/fasting). Chronodisruption has been used in the literature in generic reference to a wide variety of settings and experimental protocols (Froy & Garaulet, 2018; Galdames et al. 2014), and it can be considered synonymous with circadian disruption. Chronodisruption has also been used to refer to a specific quantitative metric, which is based on computing the overlap between an individual's biological night (approximated by sleep timing information) and work hours (i.e., work timing, including "associated activity windows" of usually 2 hr prior to work start and after work end (Erren & Reiter, 2009).

7. CHRONOBIOLOGY AND DISEASES

Nearly four decades ago, Horne & Ostberg published a milestone study on possible individual differences in circadian attitudes (Horne & Ostberg, 1976). They presented a self-assessment Morningness-Eveningness (M/E) questionnaire, consisting of 19 items with a definite score each, identifying five categories: definitely Evening type or M-type (16-30), moderately Evening type or E-type (31-41), neither type (42-58), moderately Morning type (59-69), and definitely Morning type (70-86). M-types showed a significantly earlier body temperature peak time than E-types and tended to have a higher daytime temperature, whereas I-types had temperatures between the two groups. Such a circadian individual preference was defined 'chronotype'. Evening types are also defined as 'owls', and Morning type as 'larks', and chronotype may deeply impact on working activity (Lopez-Soto et al. 2019).

As seen before, light-dark alternation has always been the strongest external circadian "zeitgeber" for humans. Due to its growing light abuse, our society is quickly going forward towards a progressive "eveningness", with consequences on individual chronotype, aldo with differences by gender. Fabbian et al. reviewed the available evidence of possible relationships between chronotype and gender, with relevance on disturbances that could negatively impact general health (Fabbian 2016). Results were grouped into four general areas, i.e. (a) "General and Cardiovascular Issues", (b) "Psychological and Psychopathological Issues", (c) "Sleep and Sleep-Related Issues" and (d) "School and School-Related Issues". (a) E-type was associated with unhealthy and dietary habits, smoking and alcohol drinking (in younger subjects) and with diabetes and metabolic syndrome (adults); (b) E-type was associated with impulsivity and anger, depression, anxiety disorders and nightmares (especially in women), risk taking behavior, abuse of alcohol, coffee and stimulants, psychopathology and personality traits; (c) E-type was associated, in young subjects, with later bedtime and wake-up time, irregular sleep-wake schedule, subjective poor sleep, school performance and motivation, health-related quality of life; (d) E-type was associated with lowest mood and lower overall grade point average (especially for women) (Fabbian et al. 2016).

7.1. Periodicity of acute diseases

The symptom intensity and mortality of human diseases, conditions, and syndromes exhibit diurnal or 24 h patterning (Smolensky et al 2015a, 2015b), and our group actively participated in the demonstration of temporal windows for many of them (Manfredini et al. 1994, 2000, 2001, 2002, 2004, 2011, 2012; Gallerani 2001; Lopez-Soto et al. 2015, 2016). Particular attention has been dedicated to cardiovascular diseases, eg, acute myocardial infarction (Muller et al. 1985; Manfredini et al. 2004), pulmonary edema (Manfredini et al. 2000); aortic aneurysm rupture or dissections (Manfredini et al. 1999; Mehta 2002; Manfredini et al. 2004), venous thromboembolic disease (Gallerani et al. 1992), and hemorrhagic and ischemic stroke (Gallerani et al. 1994, 1996; Manfredini et al. 1997, 2005). A close relationship between time and onset of certain acute diseases is extremely intriguing and fascinating.

The CV system, and most CV functions, are organized according to a specific circadian order. On one hand, predictable-in-time differences in the physiological status of the CV system may give rise to rhythmic variations in the susceptibility of human beings to morbid and mortal events. On the other, predictable-in-time differences exist in the overt expression and severity of diseases as well (Portaluppi et al. 1999). It is well known that CV events do not randomly occur, but respect peculiar temporal patterns that vary with time of the day, the day of the week, and the month of the year. In fact, when peak levels of critical physiologic variables, such as BP, heart rate (HR), sympathetic activation, and plasma levels of endogenous vasoconstricting substances, are aligned together at the same circadian time, the risk of acute events becomes significantly elevated such that even relatively minor and usually harmless physical and mental stress and environmental phenomena can precipitate dramatic life-threatening clinical manifestations (Manfredini et al. 2013).

There is a close relationship between BP rhythms and temporal patterns of cardiovascular events (Manfredini et al. 1996). BP reaches peak values in the morning, and then shows a smaller secondary peak in the afternoon. Plasma norepinephrine level and plasma renin activity are elevated in the morning; both hormones have potential to induce coronary vasoconstriction. A circadian rhythm in vascular basal tone is also demonstrated in relation to increased α-sympathetic vasoconstrictor activity in the morning. In addition, the circadian pattern of plasma cortisol secretion, characterized by a sharp morning rise, may contribute to increased sensitivity of arterial vessels to vasoconstrictor stimuli (Manfredini et al. 2004).

7.1.1. Acute myocardial infarction

7.1.1.1. Circadian (time of day)

Myocardial infarction (MI) exhibits highest frequency of onset during morning hours (6–12 AM) (Muller et al. 1985). It has been estimated that the incidence rate of acute myocardial infarction (AMI) onset is 40% higher in the morning period than throughout the rest of the day, and nearly 28% of morning infarctions and 22% of sudden cardiac deaths are attributable to the morning excess (Cohen et al. 1997). Moreover, time-dependent differences in clinical outcome also exist. A study by Manfredini et al. (2004) showed that fatal Mis were most frequent during morning hours (6 AM–noon), independent of age, infarct site, and peak levels of MB creatine-kinase (Manfredini R. 2004). Moreover, a retrospective cohort study found that there were fewer ACS admissions than expected during nights, but the proportion of patients with ACS presenting with ST-elevation myocardial infarction (STEMI) was 31% higher on nights (LaBounty et al. 2006).

7.1.1.2. Seasonal

Data from the National Registry of Myocardial Infarction of the United States reported 53% more cases in the winter than in the summer, and winter also had the highest frequency of fatal cases (Ornato 1996), and further confirmations were given (Manfredini et al. 2005, 2009).

7.1.1.3. Circaseptan (weekly)

Several studies indicated Mondat as a highest risk day of the week (Willich et al. 1994, Gnecchi-Ruscone et al. 1994), and a meta-analysis estimated an odds ratio of 1.19 (Witte et al. 2005). Manfredini et al also confirmed the Monday excess of MI both in the Emilia-Romagna and Veneto regios of Italy (Manfredini et al. 2009, Capodaglio et al. 2016).

7.1.2. Aortic aneurysms

7.1.2.1. Circadian (time of day)

Acute aortic rupture or dissection ranks third place position among causes of out-of-hospital sudden death in the general population (Manfredini et al. 1996). In agreement with MI, aortic aneurysms also exhibit a circadian variation, with highest risk in morning (Manfredini et al. 1999; Gallerani et al. 1997; Mehta et al. 2002). Such temporal variation can be explained by a series of pathophysiologic and potentially triggering mechanisms (Manfredini et al. 2004).

7.1.2.2. Seasonal

Most studies indicate a greater occurrence of aortic acute diseases during winter (Manfredini et al. 1997, 1999; Manfredini et al. 2008), independent of of climatic variables (Mehta et al. 2005). Moreover, mortality does not seem to be affected by seasonal (or circadian) patterns (Mehta et al. 2005). Many factors can explain such temporal pattern (Manfredini et al. 2004).

7.1.2.3. Genetic aneurysms

Marfan syndrome is an autosomal dominant connective tissue disease associated with acute aortic dissection (AAD). Based on data from two large registries, the International Registry of Acute Aortic Dissection (IRAD) and the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry, AAD was significantly more likely to occur in the winter/spring season than the other half of the year, and daytime (6 AM – 6 PM). Moreover, men were more likely to dissect during the daytime hours than women (Siddiqi et al. 2017).

7.1.2.4. Circaseptan (weekly)

Manfredini et al. reported a weekly pattern, with decreasing frequency from Monday to Sunday, in the Emilia-Romagna region of Italy (Manfredini et al. 2008). Interestingly, fatal cases showed an opposite trend with a peak on Sunday. Moreover, mortality was found to be higher in cases admitted on weekends compared with weekdays both in the Emilia-Romagna region (Gallerani et al. 2012) and in Italy as a whole country (Gallerani et al. 2013).

7.1.2.5. Meta-analysis

A meta-analysis conducted on more than 80,000 cases (42 studies) showed a significantly increased incidence of aneurysm rupture or dissection in Winter (Relative Risk, RR 1.17), in December (RR 1.14), on Monday (RR 1.21), and in the 6 AM–noon (RR 1.59) (Vitale et al. 2015).

7.1.3. Stroke

7.1.3.1. Circadian (time of day)

Since the late 80's, several studies reported a higher frequency of stroke onset during morning hours (Marler et al. 1989; Marsh et al. 1990; Kelly-Hayes et al. 1996; Gallerani et al. 1996). A comprehensive meta-analysis found that approximately 55% of ischemic strokes, 34% of hemorrhagic strokes, and 50% of transient ischemic attacks (TIAs) occurred between 6-12 AM (Elliott et al. 1998). As for ischemic stroke, it has been found that the morning preference is

independent of patients' age, sex, common risk factors, i.e., smoke, hypertension, diabetes, dyslipidemia, as well of type of stroke (Casetta et al. 2002). Interestingly, ischemic and hemorrhagic exhibit a quite similar timing of occurrence (Casetta et al. 2002a; 2002b), and share common risk factors as well (Manfredini et al. 2005).

7.1.3.2. Seasonal

Several studies have reported a seasonality in the occurrence of stroke, characterized by a winter and autumn peak for its occurrence (Haberman et al. 1981; Gallerani et al. 1993; Manfredini et al. 1997).

7.1.3.3. Circaseptan (weekly)

Monday has been found to be at highest risk of stroke (Manfredini et al. 2001, 2009, 2010), independent of the presence or not of most common risk factors (Manfredini et al. 2009).

7.1.4. Pulmonary embolism

7.1.4.1. Circadian (time of day)

Previous studies reported the existence of a circadian variation also in the occurrence of acute pulmonary embolism (Gallerani et al. 1992).

7.1.4.2. Seasonal

An autumnal/winter peak has been reported both for venous thromboembolism (deep vein thrombosis and pulmonary embolism (Manfredini et al. 1994; Boulay et al. 2001; Gallerani et al. 2004; Gallerani et al. 2007; Manfredini et al. 2009). A decade ago, a metanalysis of the available literature (about 35,000 cases) confirmed the increased incidence of venous thromboembolism in winter, with a relative risk of 1.14 (Dentali et al. 2011). Such pattern seems to be independent of risk factors and patients' comorbid conditions (Manfredini et al. 2004).

7.1.4.3. Circaseptan (weekly)

No reports are available dealing with weekly variation of pulmonary embolism, although a higher mortality has been found in patients hospitalized during weekends compared with weekdays (Gallerani et al. 2011, 2018).

7.1.5. Takotsubo syndrome

Takotsubo syndrome (TS) is characterized by transient left ventricular systolic dysfunction in the absence of significant coronary artery disease, occurring mostly in postmenopausal women after emotional and/or physical stress. Interestingly, women and men have distinct cardiovascular reactivity mechanisms for mental stress-induced myocardial ischemia (Ghadri 2018). The clinical expert consensus document (part I) summarized the current state of knowledge on clinical presentation and characteristics of TTS. Moreover, it has proposed new diagnostic criteria based on current knowledge to improve diagnostic accuracy. (Ghadri et al. 2018) In the last years, our group contributed to the studies of temporal patterns of TS (Bossone et al. 2011, Citro et al. 2009, Manfredini et al. 2009, 2010, 2011, 2014), so that chronobiology had a dedicated paragraph into the ESC Expert Document (Ghadri et al. 2018).

7.2. The weekend effect

A series of studies has reported a so called “weekend (WE) effect” for hospital admissions, referring to a higher risk for mortality for patients admitted on WE (Saturday to Sunday) than for those admitted on weekdays (WD) (Bell & Redelmaier, 2001), and many factors may potentially contribute (Fedeli et al. 2017). Gallerani et al. assessed WD or WE admissions and mortality for patients hospitalized with acute PE (Italian Health Ministry database 2001 to 2014). Admissions for PE were more frequent on Mondays (15.8%) and less frequent on Saturdays (12.2%) and Sundays (12.3%). After adjustment for age, gender, comorbidities, and presence of respiratory failure, in-hospital mortality for patients admitted on WE was greater (OR 1.15; $p < 0.001$) (Gallerani et al. 2018).

7.3. Gender effect

An analysis of 20 years of chronobiologic studies confirmed that morning hours are a critical time of onset of acute cardiovascular diseases in men and women (Manfredini et al. 2017).

7.4. Chronotherapy

A given drug may be therapeutic and safe when administered at some biological time, but subtherapeutic or poorly tolerated at another time (Manfredini 2013). CV disease has been first considered for chronotherapy (Manfredini et al. 1994). De Giorgi et al. reported the available evidence supporting the efficacy of chronotherapy.

8. SOCIAL JETLAG

The term Jetlag (Roenneberg et al. 2012; Wittmann et al. 2006) is used to refer to the challenge to the circadian system humans experience in their everyday life, work and social constraints. However, there is a quantitative definition: social jetlag is the difference between sleep timing on work and free days, and this represents a proxy for circadian misalignment.

Social jetlag, like chronodisruption, is a system level metric, that does not allow for multi level insights, potentially missing relevant organ, tissue or cellular levels of misalignment. The term Social Jetlag (SJ) was used by Roenneberg et al (Wittmann et al. 2006) to describe the mismatch between internal and external time. Thus, they proposed assessments of sleep timing on work free days and days that are constrained by work, school or other social obligations. This assessment can be performed via questionnaires such as the MCTQ (Roenneberg et al. 2003b), or its shift work version (Juda, Vetter, & Roenneberg, 2013b), but the same information could also be extracted from sleep logs or actigraphy data if daily work schedule information is gathered in addition to sleep behavior. Since sleep timing is regulated, in part, by the circadian system (Borbely et al. 2016; Daan, Beersma, & Borbely, 1984), it can be used as a tool to approximate inter individual differences in circadian phase. Sleep on work free days is considered to reflect the natural sleep cycle, and thereby serves as a proxy for internal time, while workday sleep is thought to be more reflective of external, social time, due to its constrained nature. The difference between workday and free day sleep timing is used to compute SJ. Again, if societal constraints are identical across individuals, results will reflect inter individual differences in sleep timing (or chronotype). In case of variable work and school start times, however, this metric incorporates potential variability in both, exposure and phenotype level, and provides a single metric estimation of the individual level of disruption on a systemic level. In crossmsectional studies, social jetlag has been shown to be associated with body mass index (Parsons et al. 2015; Roenneberg et al. 2012), and biomarkers of cardiometabolic health (Rutters et al. 2014; Wong et al. 2015), but prospective studies are currently missing. While useful, this metric also has limitations: (a) it solely captures system level output, and we have no insights into how social jetlag relates to internal phase relationships or molecular level rhythms; (b) in individuals with sleep disorders, or otherwise disrupted sleep behavior, this metric is likely to be flawed (Suh et al. 2017); (c) as it is an aggregate measure, it omits potential informative time series information, such as variation within free days or within work days; and finally (d) while social jetlag approximates current levels of circadian disruption, and thereby is useful to track the effects of, for example, work schedule or lifestyle interventions (e.g., Vetter et al. 2015), there is currently no formal way to estimate cumulative, lifetime exposure. This is an important challenge

that will need to be addressed, as such a metric is crucial to identify biomarkers of chronic circadian disruption (Mullington et al. 2016). Changes in circadian phase over the lifespan (Crowley et al. 2014; Roenneberg et al. 2004), as well as changes in work schedules and other environmental challenges over time, contribute to the difficulty of estimating a cumulative lifetime exposure.

9. SHIFT WORK

In general, humans are day active, so that working during the biological night is considered the maximal challenge to the circadian system. However, when individuals report on their night shift work history, assessments also implicitly capture multiple factors that are usually used independently as exposures in animal studies. Working during the night is correlated with light exposure during the night, nighttime eating and caloric intake, being awake and active at times when we usually sleep, daytime sleep (which in turn reduces sleep quality and reduces sleep duration (Åkerstedt et al. 2003), especially in individuals with an early chronotype (Juda et al. 2013a), as well as consuming stimulants at night, such as cigarettes and caffeine. While night shifts represent the most strenuous shift for most individuals, early morning shifts (i.e., shifts starting before or at 6am) can also be a burden: depending on commute and start times, individuals sometimes have to awaken as early as 3:30 a.m. to be at work at 6:00 a.m. Such early wake up times end the sleep phase for the vast majority of individuals during their biological night, disrupt sleep (Åkerstedt, Kecklund, & Selén, 2010), and have been shown to impair insulin sensitivity (Eckel 2015). Identifying the contribution of the necessary and sufficient drivers of adverse health effects of shift work is a key to designing efficient and effective prevention and intervention strategies. Is it, for example, sufficient to shift meal and caloric intake entirely to the biological day to prevent disease or improve metabolic function, or is it necessary to couple interventions (e.g., adjunct sleep, light, and meal time interventions) to achieve the desired effects? Because shift work is necessary, especially in the health care, transportation and security sensitive sectors, the need to design effective prevention strategies is high.

Shift work studies now increasingly assess and report the multiple dimensions of work schedules, including timing and duration of shifts, direction of rotation, number of consecutive shifts, weekly work hours, and time between shift transitions. This level of descriptive and analytical detail is required for the development of medical guidelines and the refinement of individual and organizational prevention and intervention strategies (Papantoniou, Vetter, & Schernhammer, 2016). Shift work assessment now increasingly reflects more adequately the variable nature of the exposure. Taken together, shift work in general has been widely used as a proxy for circadian

disruption, but only recently have studies started to collect work schedule information reflecting the multi dimensionality of schedules. These types of assessments, however, still do not account for inter individual variability in circadian and sleep phenotypes. Juda et al. proposed to use SJ (Juda et al. 2013b) or composite phase deviations (Fischer et al. 2016) as a proxy for misalignment in shift workers to obtain a higher resolution, single unit estimate of the disruption an individual experience in a given schedule, while others have suggested that chronodisruption (Erren & Reiter, 2009) might be a better way to incorporate inter individual differences in sleep and circadian phenotypes into exposure assessment (Kantermann et al. 2010). Yet these remain activity-based proxies for circadian disruption, as we still lack direct measures of circadian clock disruption that are non invasive, low burden, and scalable to epidemiological samples (because DLMO is not feasible on cost and logistical grounds in such large samples), although there are clear and promising efforts in this direction (Braun et al. 2018; Laing et al. 2017; Wittenbrink et al. 2018). Until such measures are shown to be robust in field settings, future shift work studies should consider deriving multiple measures of circadian disruption to also capture much needed insights into organismal and molecular consequences of shift work, especially in real life, community based settings. A study in individuals working morning and evening shifts tracked average wake times, mealtimes and peak times of clock gene expression from hair follicle cells (Akashi et al. 2010) and showed a shift in meal and wake times by about 7 hr when transitioning from morning to evening shifts, but clock gene peaks shifted by 2 hr, and the authors conclude that the 1 week of evening shift was not sufficient for adaptation.

10. DAYLIGHT SAVING TIME

The idea of introducing daylight saving time (DST) was originally born to save energy. Today, only a small fraction of electricity expenditure actually corresponds to producing light after sunset (in the US, it is about six percent in the residential sector and eight percent in the industrial sector) (US Energy Information Administration, 2016). Yet, over a quarter of the world population is subjected to the DST shift twice a year, which disrupts both human work and rest schedules and possibly their circadian clock rhythms (Kantermann et al. 2007). Previous studies have demonstrated that the spring DST shift causes noticeable alterations in human behavior in terms of waking-up time and self-reported alertness (Mink & Folkard et al. 1976), a significant increase in fatal traffic accidents (up to 30 percent on the day of commencing DST), (Prats-Uribe et al. 2018) a short-term rise in workplace injuries (5.7 percent after the spring DST shift as employees sleep 40 minutes less on average), (Barnes & Wagner, 2009) and elevated rates of acute myocardial infarction (up by about

3.9 percent) (Janszky et al. 2012; Manfredini et al. 2018, 2019). Different authors reported conflicting results regarding whether the DST shifts are associated with accident incidence (Prats-Uribe et al. 2018; Lahti et al. 2008). Heboyan (2019) reported increased mental health- and behavioral health-oriented emergency department visits in certain seasons but did not obtain conclusive results on whether they could be linked to the DST shifts. Remarkable progress has been made in the past decade towards understanding the neurology of sleep-wake cycles and circadian rhythms, and how they affect our behavior (Fuller et al. 2006). An increase in AF hospital admissions was found following the DST springtime transition (Chudow et al. 2020). Despite these advances, significant gaps remain in our knowledge of how changes in the social clock (DST shifts) interact with the body's biological clock and impact human health. Recent studies have urged for investigations into the clinical implications of DST shifts on human health (Roenneberg et al. 2019; Malow et al. 2020). On the other hand, the position of the American Academy of Sleep Medicine states that DST should be abolished in favor of a fixed, national, year-round standard time (Rishi et al. 2020). Zhang (2020) evaluated the effect of the DST shift on a whole spectrum of diseases. They performed a population-based, cross-sectional analysis of the IBM Watson Health MarketScan insurance claim dataset, which incorporates over 150 million unique patients in the US, and the Swedish national inpatient register, which incorporates more than nine million unique Swedes. For hundreds of sex- and age-specific diseases, we assessed effects of the DST shifts by comparing the observed and expected diagnosis rates after DST shift exposure. Four prominent, elevated risk clusters, including cardiovascular diseases (such as heart attacks), injuries, mental and behavioral disorders, and immune-related diseases such as noninfective enteritis and colitis were found to be significantly associated with DST shifts in the United States and Sweden. While the majority of disease risk elevations are modest (a few percent), a considerable number of diseases exhibit an approximately ten percent relative risk increase. Authors estimated that each spring DST shift is associated with negative health effects–with 150,000 incidences in the US, and 880,000 globally. Authors also identified a collection of diseases with relative risks that appear to decrease immediately after the spring DST shift, enriched with infections and immune system-related conditions.

11. CIRCADIAN RHYTHM & OBSTETRIC ASPECTS

In the obstetrics fiel, all the above functions play an important role for maternal-child well-being, as well as for the correct fetal development and for the onset of spontaneous labour. There is still an

unavaused question from epidemiology and obstetrics, the reason why it is precisely at a give moment that the labour of spontaneous childbirth begins.

Scientific evidence suggests that the role of stress hormones may be fundamental, and in particular the placental corticotropin releasing hormone (CRH). It would serve as a “placental clock”; it is active from the earliest periods of pregnancy and determines its duration, the time of onset of labor and the timing of childbirth.

In the last decade of the last century the presence of CRH has been demonstrated already in early times, i.e. at 16-20 weeks, in addition to the fact that its concentration during pregnancy is indicative of the gestational period of the delivery (preterm, post-term or term), but above all it has been shown that plasma levels of bioavailable CRH increase rapidly near the onset of spontaneous labor. This data suggests that this hormone may play a pivotal role in activating the mechanism of labor (McLean et al. 1995).

11.1. The chronobiology in Obstetrics

In Obstetrics all the placental functions play an important role in maternal and neonatal health as well as for the correct fetal development and for the onset of labour. Nowadays there is a question not answered by Epidemiology and Obstetrics, the reason why just at a certain time the spontaneous labour begins. Evidence suggest that stress hormones could be determinant and in particular the placental Corticotropin Realising Hormone (CRH). It has the function of “placental watch”; it’s active from the first periods of pregnancy and it determines its duration, the timing of the labour onset and of the delivery. In the last decade of the past century the presence of CRH just in early periods, or at 16-20 weeks, as well as its concentration during pregnancy are indicative of the gestational period of delivery (preterm, post term or at term) but expecially it has been evidenced how the plasmatic levels of bioavailable CRH rapidly increase near the beginning of the spontaneous delivery. This data suggests that this hormone can play a pivotal role in the activation of the mechanism of labour and delivery. These phenomena have been demonstrated by a cohort study by McLean published in Nature in 1995 (Figure 1). It recruited 485 pregnant women at the first trimester to be subjected to serial blood tests during the three trimesters to evaluate the CRH plasmatic concentrations and relate them to the gestational period of delivery. Among the total sample, 308 women gave birth at term (between 37 and 42 weeks), 24 preterm (before the 37th week) and 29 post term (after the 42nd week). In the Graphics A and B of the Figure 1, the continuous line represents the average of CRH values, expressed in median value multiple of

mediam (MoM), of the women with a term delivery. As we can see in the Graphic A, in case of preterm birth, the CRH values are above the broken line during the whole pregnancy (3,64 MoM ± 0,55, p=0.0009), while in case of post term birth they are below (0,97 MoM ± 0,16, p=0.004) (Graphic B). The Graphic C has been created by the linear regression calculated on the CRH values in pregnancy related to the gestational period of delivery. So, three distinct lines have been created, the first represents the CRH values during the various gestational periods in women with a preterm birth, the second in women with a birth at term and the third with a post term delivery. It's so evident how the line of the preterm birth moves towards the left of 6 weeks compared to the term birth one, while the post term birth line moves towards the right of 2 weeks. This demonstrates the correlation between plasmatic CRH values and the gestational period of the delivery. Finally, the Graphic D represents the trend of the CRH plasmatic concentration during pregnancy. It's therefore possible to note how near the term of pregnancy an important increase is present. Many are the factors affecting the placental CRH secretion. Among them we find prostaglandins, glucocorticoids, cytokines and catecholamines increasing its secretion while nitric oxide inhibits its secretion. Other elements that can change the plasmatic CRH concentrations are genetic predispositions and maternal or fetal pathologies.

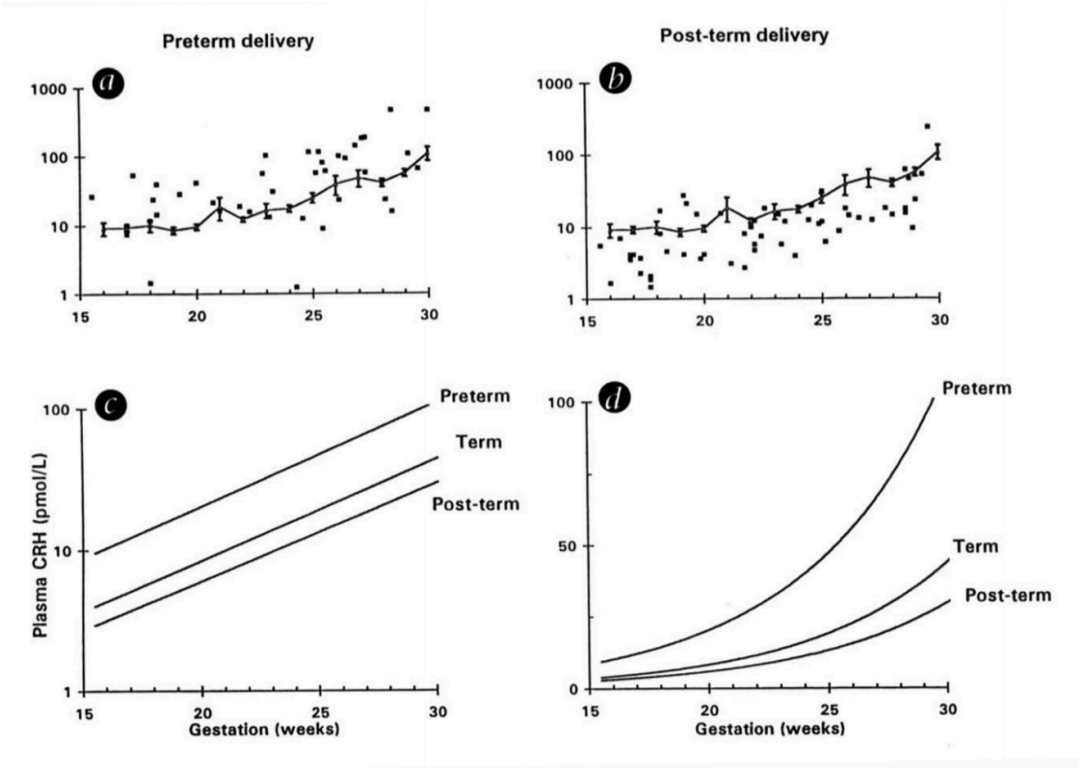


Figure 1. *CRH secretion and labour activity. Adapted from: McLean et al. (1995)*

Sleep disorders and the circadian rhythm alterations can lead to an increased stress hormones levels and the activation of a proinflammatory condition some time (Spiegel et al. 1999) it starts and powers up the activity of 77aesarean77ers77 and 77aesarea that induce the uterine contractions, the 77aesare phenomena and then the onset of labour. These alterations can be induced in the body after the performing of shift work, classic example of the circadian rhythm alterations. In fact, it has been demonstrated that women with a continuous alteration of the circadian rhythm because of their work, are significantly more exposed to a reduction of fertility rate and a lower neonatal weight at birth (Laugsand et al. 2012). The Chinese retrospective study, published in 2011 (Yu-Cheng et al. 2011) demonstrating this phenomenon, analyzed a 440 women sample, employed in a manufacturing industry in the decade 1997-2007. The sample was stratified into three exposure classes, determined by the women' answers reported by the questionnaire administered to them for the survey. The three classes were identified according to the working hours in the 5 years before of the questionnaire administration and classified in this way:

1. Daily work
2. Shift work: during 24 hours
3. Intermittent shift work: who had been working for a year at least and then has been assigned to a daily work.

Thus, the population analyzed had an average age of 28.4 years. Among the 440 selected women, 111 gave birth to 158 babies (81 males and 77 females). The analyzed data from the birth certificates allowed to relate the mother's working hours to the neonatal weight at birth (Figure 2). In particular, it's possible to notice that the 45% of women steadily working on shift gave birth to neonates with a weight between 1950 g and 2834 g, while only the 26% of women working daily had newborns with that weight. On the contrary, considering the opposite weight class at birth (3520-4768 g), the percentages are reversed: only the 12% in case of women working on shift while the 49% in case of women only working daily (OR 1.7; 95% CI 1.01 – 3.0).

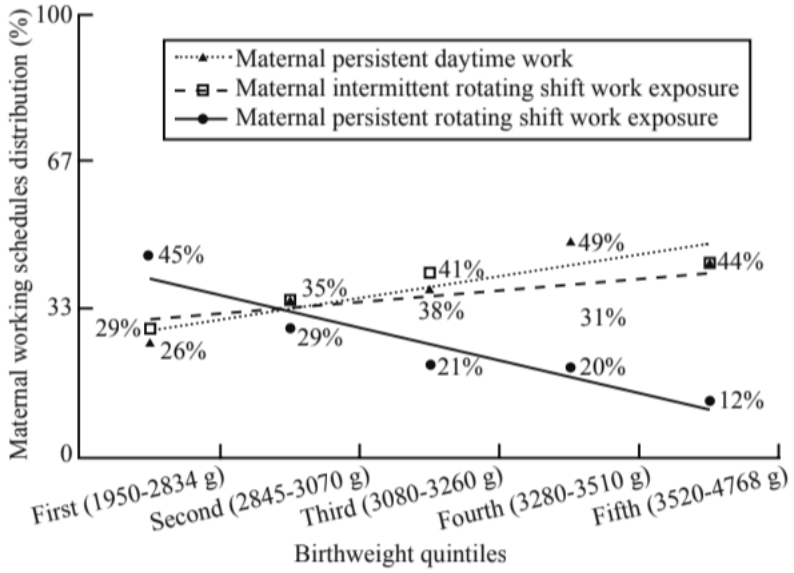


Figure 2. *Correlation between birth weigth classes and the type of work of the mother. Adapted from: Yu-Chen et al. (2011)*

7.1. The role of 78aesarea in the rhythmicity of delivery

It's well known that 78aesarea is the prince hormone allowing the onset and the continuation of labour. Many studies on animals have been carried out to evaluate if 78aesarea affect the circadian rhythmicity observed at the time of delivery. Some studies on rodents (Reppert et al. 1987) had already demonstrated that the moment of the day of delivery depended on the suprachiasmatic nucleus of hypothalamus, the same centre controlling the circadian rhythm too. For this reason, it was imagined that it could be hardly influenced by the circadian rhythm itself, unlike the duration of pregnancy about which the central nervous system control was excluded (Miller et al. 2004). In the cited studies, the rodents observed after the injures of the central nervous system gave birth anyway at the same gestational period of the rodents with an intact central nervous system. Really an American study in 2007 (Roizen et al. 2007) showed that 78aesarea secretion during pregnancy has its rhythmicity that is not the same of the circadian rhythm and it's not influenced by it. This led to the conclusion that 78aesarea secretion is regulated by a pacemaker different and well distinct from the central circadian watch instead controlling the motor activity and many other human activities. The pacemaker controlling 78aesarea secretion defines the rhythmicity of the timing of delivery. This has been observed by the RCT published by Roizen J. in which 78aesarea serum levels of the not genetically modified rodents were measured. The RCT was carried out on an animal sample. A group of mice have been genetically modified to disable them to produce 78aesarea. Another hormone significantly affecting the timing of delivery is melatonin **(**Olcese et

al. 2012). This hormone plays a key role in the circadian rhythm regulation too. Melatonin is a fat-soluble hormone produced and released by the epiphysis into the bloodstream in response to the information received by the central circadian watch. Synthesis and secretion of melatonin happen in the phase of dark of the day and are inhibited by the human eye exposure to the light. Their receptors are present in several reproductive tissues among which endometrium and myometrium. The way by which the hormone acts on these cells is not completely known by the scientific community. What is certain is that melatonin has a species-specific effect on uterus and so it behaves as antagonist of 79aesarea in some species while in others, as humans, with a 79aesarea action (Olcese et al. 2014). In the myometrium, in the human species, melatonin and 79aesarea recruit mechanisms of intracellular reports, extremely similar each other and both functional to the onset and the continue of the spontaneous labour (Sharkey et al. 2007). Sharkey in his study in 2009, showed that 79aesarea and melatonin receptors are both present in the myometrium but with higher concentrations in women with contractions, compared to women without them.

An American study in 2014 confirms the synergy between the two hormones and their key role in the onset of labour. It assessed the continuity and the characteristics of contractions, related to the seric melatonin concentration, in voluntary pregnant women at term (between the 39th and the 40th gestational week), randomized into two groups, only one of them exposed to an hour of light at night. The study is a pilot clinical trial. The sample was composed by 18 voluntary pregnant women between the 39th and the 40th week, divided into two groups: the exposure group composed by 15 women and the control group by 3 women. They were all tested with external tocodynamometry to evaluate the uterine contractions from 7 p.m. to 7 a.m. The exposure group was subjected to a white light, positioned at 1 meter from human eyes at 11 p.m. Blood tests were done to the whole sample every hour to evaluate the seric melatonin levels. In the group exposed to the light source, the seric melatonin levels crashed in the hour after and then increased slowly and progressively ($p<.0,5$, Student's Test), until reaching overlapping values to that of the not exposed group after 4 hours. About the characteristics of the contractions a similar trend was revealed: absence of the contractile activity followed by their resumption. It's possible to see in the four graphics below what just explained (Figure 3). The Graphic A shows the seric melatonin levels identified in the sample. The broken blue line represents the group exposed to the light while the red broken line represents the control group. The indicator on 11 p.m. is the reference of the beginning of the case group exposure to the sun light. We can see, therefore, how, after the exposure to the light, the blue broken line has a rapid deflection caused by the sudden reduction of the seric melatonin values of over the 40% ($p<.05$, Student's Test) and then it progressively resumes and reaches the red broken line on 4 a.m. On the contrary the Graphics B, C and D represent the trend of the contractile activity. The

Graphics C and D show that after the exposure to the light there are not contractions for two hours and then they start again. The study has an important bias, the sample dimension, really small. Neverthless, the results allow to imagine a direct correlation between the seric melatonin concentration and the contractile activity. Considering the impact on the sleep-wake cycle in the transition from the solar time to the daylight saving time and the other way around, it's possible to imagine that this change of time also affect the melatonin secretion, modifying it. So it's possible to imagine the feedback of a reduction of the contractile activity in the first days after the transition, related to a reduction of the number of spontaneous deliveries.

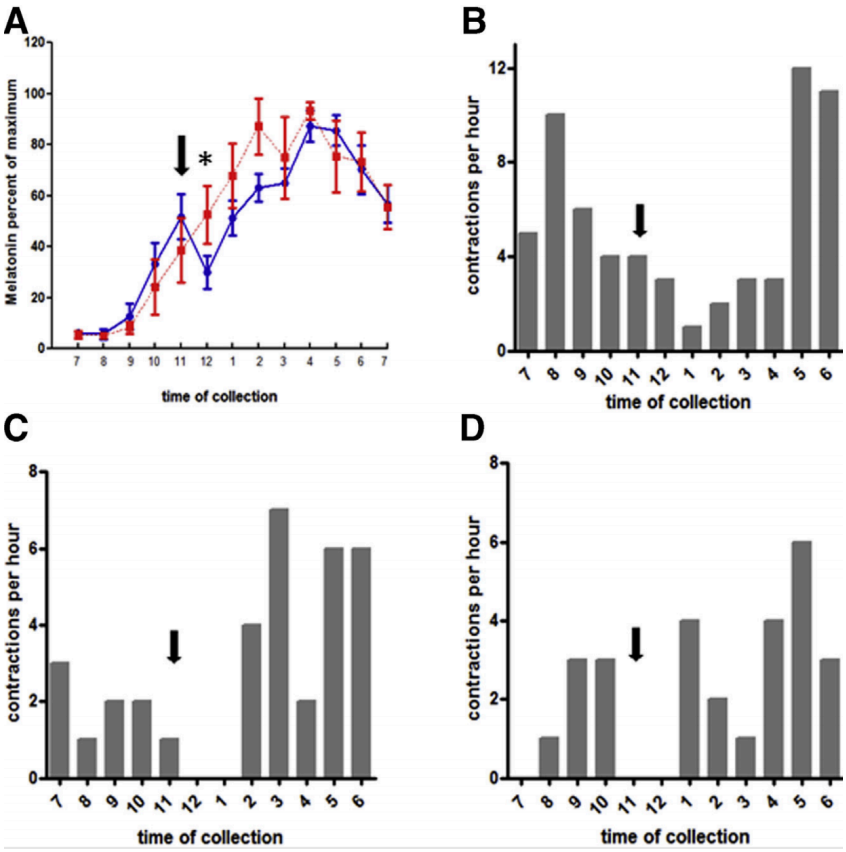


Figure 3. *Synergy between the melatonin-xoytocin and their key role in the onset of labour. Adapted from: Olcese & Beesley (2014).*

12. SLEEP CHANGES DURING PREGNANCY

Pregnancy is related to many physical, hormonal and emotional changes that can affect sleep patterns, the ability to perform daily tasks and the quality of life itself. In the opinion of the National sleep (2007), the 795 of pregnant women suffers from sleep disorders. The changes of sleep models during pregnancy can increase from the 13% to the 80% in the first trimester and from the 66% to the 97% in the third one. More than the 72% of pregnant women frequently experiences an awakening during the night (Rezaei et al. 2013). Among sleep disorders in pregnancy there are insomnia, Restless Legs Syndrome (RLS), sleep apnea, nocturne gastro esophageal reflux desease (GERD), backhache, urinary urgency and higher frequency at night.

12.1. First trimester

Sleep disorders already begin in the first trimester, probably due to the rapid changes of the reproductive hormonal levels. Progesterone levels increase during pregnancy. At the 36th week they are ten times higher than the menstrual cycle peak levels. In the studies carried out on animals, the authors observe that progesterone administration has sedative effects to reduce wakefulness, the latent phase and increase the duration of slow-wave sleep (NREM) (Lancel et al. 1996). During pregnancy, hypersomnolence is common in the first trimester and daytime naps are frequent because of the fatigue. In this period, the data on women surveyed about their sleep habits report an average increase of 0,8 hours (on average from 7,4 to 8,2 hours) of sleep duration during the first trimester compared to the pre-pregnancy period (Reichner et al. 2015a). Likewise, an average increase of more than 30 minutes of night sleep has been observed at 11-12 gestational weeks in 33 women submitted to domestic polysomnography before the conception and during every trimester of pregnancy. During the first trimester the phase 1 of NREM sleep increases while the phase 3 of NREM sleep decreases and the efficiency of sleep decreases compared to the pre-pregnancy period (Reichner et al. 2015b). In the first period the most common causes of bad sleep are nausea and vomit, urinary frequence and backhache.

12.2. Second and third trimester

Near the end of the second trimester (23-24 gestational weeks) the total time of night sleep decreases compared to the first one (from 6,6 to 7,8 hours). During the third trimester, the most of women has difficulties to sleep, more than the 98% reports night awakenings. From the first trimester there is a progressive reduction of the percentage of NREM sleep phase 3 and REM sleep,

and an increasing NREM sleep phase 1. Despite the increase of the time of wakefulness and the reduction of the time of the night sleep compared to the first two trimesters, the total sleep time becomes quite normal as the pre-pregnancy sleep levels. There is no evidence of changes of the circadian rhythm when the levels of melatonin show the daytime rhythm. In the third trimester, sleep disorders are due to a general discomfort caused by backhache, urinary frequency, fetal movements, GERD, stomach hache, legs cramps and tingling (RLS) and dyspnea (Hashmi et al. 2016).

12.3. Effects of sleep deficiency

The change of sleep models induces some difficulties in the daily habits, maternal fatigue, loss of familiar wellness; the lack of sleep affects physical and mental health. Moreover, the decrease of psychological relaxation induces an increase of anxiety as well as the fear of taking care of the newborn and the acceptance of the maternal role in the family (Rezaei et al. 2013).

In pregnancy, sleep disorders like the short duration and the poor efficiency of sleep show a relation with an increase level of interleukin-6, C-reactive protein and higher levels of serum proinflammatory cytokines (Okun et al. 2007).

Sleep deprivation induces a decrease of the immune system function, of hypothalamus, of the pituitary gland and of the adrenal glands. Moreover, it causes the reduction of glucose tolerance, hypertension and an indirect increase of cardiovascular risk.

The short duration of sleep, assessed by the questionnaires on sleep, can increase gestational diabetes (GD) with a relative risk ratio of 5.6 among the women sleeping less than or 4 hours at night compared to 9 hours (Qiu et al. 2010): every hour of sleep is related to a 4% glucose increase and a sleep duration lower than 7 hours a night increase the GD risk (Reutrakul et al. 2011). These studies are based on subjective data rather than objective one. The sleep duration lower than or 6 hours a night at the beginning of pregnancy is related to an increase of the average blood pressure in the third trimester (Williams et al. 2010). With a sleep reduction, a poor sleep quality can affect the pain perception with a lower ability of women to cope with labour (Beebe et al. 2007). Poor sleep is related to an increased risk of emergent 82aesarean section too (OR 1.57, IC 95% 1.14-2.16) (Wangel et al. 2011). In 457 women filling in the questionnaires about sleep, the effects of sleep duration and its quality on labour and on fetal outcomes have been assessed considering the labour duration, the newborn weight and the Apgar score (score assigned to the newborn at the 1st and the 5th minute after birth to assess his clinical conditions after intrapartum stress. 5 components are

assessed: skin colour, reflexes, muscle tone, heart and respiratory rate. To each of these, a score from 0 to 2 is assigned with a total maximum score of 10; a score higher than 7 reveals a healthy newborn). The women sleeping more than 8 hours a night have experienced a shorter first period of labour, from 6 to 10 hours compared to higher than or 10 hours (p= 0,029), and most of newborns of women sleeping more than 8 hours had an Apgar score higher than 9 (p= 0,001). Moreover, the mothers with restful sleep had newborns with a weight higher than or 2500 g (p< 0,001) (Zafarghandi et al. 2012). The sleep duration lower than 8 hours increases the risk of low birth weight (OR 2,84, IC 95% 1,49-5,40) (Abeysena et al. 2010). The women with sleep deprivation (≤5 hours a night) reveal a higher risk of preterm birth (1,7 IC 1,1-2,8) (Micheli et al. 2011). Some studies about sleep disorders in pregnancy indicate an increased risk of operative delivery, depression during pregnancy and in postpartum, as well as a negative impact on families and on society.

12.4. Sleep-wake cycle in the fetus

In the fetus and newborn, sleep is classified in active sleep and quiet sleep. Active sleep becomes REM in the baby and in the adult while the quiet sleep is NREM.

The rhythmic cycle of the period of activity and rest can be identified in the human fetus between the 28th and the 32nd gestational week. Neither the quiet sleep (NREM) nor the active sleep (REM) can be identified in preterm newborns between the 24th and the 26th gestational week. From 28 to 30 weeks, the active sleep can be recognized by the presence of eye and body movements. The quiet sleep cannot be clearly identified in this period (active sleep includes the most of sleep period), in fact it doesn't seem to be significantly revealed until the 36th gestational week. Once identifiable, this state keeps increasing regularly until becoming the dominant state at about postnatal 3 months (Sheldon et al. 2014). In the third trimester it becomes possible to recognize some real fetal behavioural states based on the evaluation of the heart rate, body and eye movements. These last one can be identified and classified as:

- state 1F (or quiet sleep, NREM): it's a quiescent state with a long- term close variability of the fetal heart rate;
- state 2F: it's characterized by gross body movements, 83aesarean83 eye movements, wide variability of the fetal heart rate. It's about a similar state to REM phase or to the newborn active sleep;

- state 3F: it's characterized by 84aesarean84 eye movements without body movements and fetal heart rate accelerations;
- state 4F: it's characterized by vigorous body movements with 84aesarean84 eye movements and fetal heart rate accelerations. It corresponds to newborn waking state.

Most of time the fetus lives in the states 1F and 2F; at 38 weeks he is in these two states for the 75% of time. Moreover, there is sleep-wakefulness cyclicity, varying from 20 to 75 minutes (Borrelli et al. 2008). From the fifth month there is already a circadian organization: at the end of the day the fetus begins moving. These movements, repeating every day, show a synchronization with alternating day and night. This rhythmicity is probably controlled by the suprachiasmatic nuclei of the future baby, found in the human fetus at the 18th gestational week. These rhythms depend on the maternal 84aesarean84ers, mostly on maternal secretion of cortisol and melatonin. Maybe the fetus is also sensitive to the maternal sleep-wake regularity (Challamel et al. 2018). During pregnancy, the melatonin circadian rhythm passes through the placenta and affects the circadian development and maturation of the fetal central nervous system. The regular perturbations of the light-dark cycle, contaminating the night with artificial light, undermine the circadian watch and inhibit the night rise of melatonin, both are normally important for the developing fetus. The implication of this finding is that during pregnancy, in particular during the last trimester, a rather regular undisturbed light-dark cycle should be kept improving and strengthen the circadian rhythms and to preserve the melatonin cycle (Reiter et al. 2014).

13. DAYLIGHT SAVING TIME AND SPONTANEOUS DELIVERIES

The mechanism that starts the spontaneous onset of labor still remains an unanswered 84aesarean In the current literature (Wilcox et al. 2010). In the obstetric field, scientific research is rich in studies, conducted both in vitro and in vivo, explaining the action of hormones in the onset and maintenance of labor during birth by correlating it with the circadian cycle (Lincoln & Porter, 1976). Cortisol is the main stress hormone responsible for the normal adaptation of the neonate to extrauterine life. Placental corticotrophin releasing hormone (CRH) is active from the early weeks of pregnancy and determines its duration, the time of onset of labor, and the timing of delivery; moreover, its plasma levels increase rapidly near the beginning of spontaneous labor. Data suggest that CRH may have a pivotal role in activating the mechanism of delivery (McLean et al. 1995; Spiegel et al. 1999; Laugsand et al. 2012). In addition, type of delivery, e.g., vaginal or caesarean, may determine a different stress response. Recently, a study compared the activity of 11beta-hydroxysteroid dehydrogenase type 2 (11β-HSD 2) in the placenta and the umbilical cord blood cortisol level

between caesarean sections, with or without uterine contraction, and vaginal delivery groups (Słabuszewska-Jóźwiak et al. 2020). No statistically significant differences in the activity of 11β-HSD 2 were found in placentas delivered via caesarean sections compared to vaginal deliveries, while umbilical cord blood cortisol in the elective caesarean sections group was significantly lower compared to the vaginal deliveries and intrapartum caesarean sections (Słabuszewska-Jóźwiak et al. 2020). Sleep disturbances and alterations in the circadian rhythm can lead to an increase in the levels of stress hormones and the activation of a pro-inflammatory condition can trigger and enhance the activity of prostaglandins and oxytocin, by promoting uterine contractions, the dynamic phenomena of labor, and consequently, the onset of labor (Spiegel et al. 1999; Laugsand et al. 2012; Słabuszewska-Jóźwiak et al. 2020; Hernández-Díaz et al. 2014). These alternations can also be induced by shift work; in fact, women who experience an alteration of their circadian rhythm due to work are significantly more exposed to a reduction in birth rate and a lower birth weight of their newborns (Lin et al. 2011). The purpose of the so-called "Summertime" was to capitalize on natural daylight: by turning the clock one hour forward as the days get longer in Spring, sunset is delayed by this same hour, until the clock is set back again in Autumn. After a first phase of Daylight Saving Time (DST) policy, where single countries decided their own standards, not regulated, harmonization attempts began in the 1970s to facilitate the effective operation of the internal market, and this practice is applied in over 60 countries worldwide [www.europarl.europa.eu]. Since light–dark alternation influences the synchronization of circadian rhythms of most human systems, DST may cause a chrono-disruption by significantly altering circadian rhythm and negatively influencing sleep quality (Manfredini et al. 2018). A growing amount of evidence showed that DST transition may have negative effects on health (Zhang et al. 2020; Manfredini et al. 2019, Manfredini et al. 2019; Chudow et al. 2020; Malow et al. 2019; Heboyan et al. 2019). Thus, based on these premises, an international consensus statement suggested that DST cannot be encouraged and therefore, should be discontinued (E Cruz et al. 2019). As for female reproduction, disruptions of circadian rhythms, e.g., shift work, jet lag, and DST, have been associated with poorer fertility and early pregnancy outcomes (Mills & Kuohung, 2019). However, very few data are available on the effect of DST on the onset of spontaneous labor. Only one recent published study showed no significant association between DST circadian rhythm and the number of spontaneous deliveries (László et al. 2016).

14. MIDWIFERY AND CHRONOBIOLOGY

14.1. Relationship between chronotype, shift work, and risk of medication errors among Italian midwives

Chronobiology is a biomedical discipline devoted to the study of biological rhythms. Biological rhythms exist at any level of living organisms and, according to their cycle length, are classified into: (a) circadian rhythms (from the Latin circa-dies, characterized by a period of ~24 h), (b) ultradian rhythms (period <24 h), and c) infradian rhythms (period >24 h) (Manfredini et al. 2007). Circadian rhythms are the most commonly and widely studied biological rhythms, but they are not strictly the same in all persons, since an individual circadian preference (the so-called chronotype) closely linked to biological and psychological variables, exists. Horne & Ostberg first described possible individual differences in circadian attitudes, the so-called chronotype (Horne & Ostberg, 1976). By means of a simple a self-assessment Morningness–Eveningness Questionnaire (MEQ), they identified Morning-types (M-type, more active early in the day), Evening-types (E-type, more active later in the day), and without type or Intermediate (I-type). As for chronotype distribution, data based on human population in the temperate region seem to show a Gaussian curve, with 10% M-type, 10% E-type, and 80% I-type (Ashkenazi et al. 1997). Moreover, differences by sex and age exist as well, with men on average more evening-oriented than women, although these differences reduce with time (Ashkenazi et al. 1997). In fact, young women are more morning-oriented than young men, but older women are less morning-oriented than older men (Randler & Engelke, 2019).

Chronotype. A growing body of research indicates that evening chronotype may be associated with a series of unfavourable conditions. A review from our group analysed the available literature to evaluate the relationships between chronotype, gender, and different aspects of health, such as general health and metabolism, psychological health, and sleep and sleep-related problems (Table 1) (Fabbian et al. 2016; Ki et al. 2020). As a general rule, M-types cope better with the synchrony effect than E-types and are able to adapt to unfavourable circumstances. At suboptimal times, M-types solved the analogy detection task faster, with the same accuracy and without the investment of more cognitive resources. They also showed greater alertness and wakefulness. At optimal times of day, M-types had more cognitive resources available to allocate in the case of more demanding conditions. E-types appear less able to adapt to suboptimal times, because they have to deal with social jetlag and decreased self-control (Nowack & Van Der Meer, 2018). In fact, a recent systematic review reported that female nurses with an evening-oriented preference suffer more problems of insomnia, sleepiness, fatigue, and anxiety (López-Soto et al. 2019).

Table 1. Association between chronotype and main health issues. Adapted from: Fabbian et al. (2016)

Main Health Issues	Chronotype	Main Findings
General and cardiovascular health	Evening-type	Unhealthy diet ↓ Physical activity ↑ Smoking Metabolic syndrome Diabetes mellitus
Psychological & psychopathological issues	Evening-type	↑ Common mental disorders ↑ Depression symptoms ↑ Anxiety symptoms Nightmares Risk-taking behaviour
	Morning-type	↑ Health-related quality of life
Sleep & sleep-related issues	Evening-type	Later bedtime and wake-up ↓ Sleep duration ↓ Sleep quality ↓ Sleep quantity ↓ Sleep efficiency

Note: (Symbols: ↑ Increased; ↓ Decreased).

Shift work. Circadian rhythms are entrained by the light/dark alternation and a series of desynchronizing factors, such as exposure to light at night, jetlag, shift work, and daylight saving time, play a crucial role in disrupting the individual organization of circadian rhythms. Among these desynchronizing factors, shift work certainly plays crucial role, due to the wide dissemination of social request for activities warranting 24/hours/seven days a week assistance (Sack et al. 2007). According to data from the Italian Institute of Statistics (ISTAT) survey "Working time organization: the role of atypical work schedules", shift working involves about one worker of five in Italy (20.4%). By disaggregating according to industry, social services (which includes education, health and social services, public administration) show the highest figures (26.8%), followed by manufacturing (21.9%) and trade services, including commerce, transport, and communications (21.7%). More men than women work with shifts (respectively 21.7% and 18.4%, respectively), due mainly to shift schemes which imply night work [www.eurofound.europa.eu]. Different disorders have been associated with shift work, with stress and sleep disorders as the most frequent ones. For example, when comparing nurses and firefighters with day workers, sleep disturbances were more frequent in shift workers than day workers (Choi et al. 2020). Moreover, different cardio-metabolic indices, including higher waist circumference, body mass index, fasting glucose, blood pressure, and cardio-metabolic risk score have been described in night workers

(Ritonja et al. 2019), who also showed almost three times higher association with abdominal obesity independent of age and gender than day shift workers (Brum et al. 2020).

Errors. Medications errors (Mes) represent a major concern of healthcare systems worldwide, and near misses represent the most reported incidents (69.3%) (Aseeri et al. 2020). According to the World Health Organization, near miss is defined as "an error that has the potential to cause an adverse event (patient harm) but fails to do so because it is intercepted" (World Health Organization, 2020). Although inadequate staffing levels, workload, and working in haste have been called the most frequent causes of increased risk for omissions and other types of error and for patient harm (Härkänen et al. 2020), circadian misalignment, in addition to a series of health problems in shift workers secondary to the sleep deprivation, e.g., daytime sleepiness, i.e., the difficulty maintaining wakefulness and alertness during normal waking hours (Drake et al. 2004; Arbur et al. 2019; Di Muzio et al. 2019a, 2019b), can represent a crucial favouring factor for lack of performance and any kind of errors. Attentional networks are sensitive to sleep deprivation and increased time awake, and sleep duration variability appeared to moderate the association between sleep duration with overall reaction time and alerting scores (Barclay & Myachykov, 2017). Nurses' sleep quality, immediately prior to a working 12-h shift, was shown to be more predictive of error than sleep quantity (Weaver et al. 2016) and functional magnetic resonance imaging (fMRI) studies showed that task performance in nonoptimal times of the day may result in cognitive impairments leading to increased error rates and slower reaction times (Reske et al. 2015). Moreover, sleep deprivation represents a further source of risk, not limited to the short term. In hospital shift workers, being screened positive for a sleep disorder was associated with 83% increased incidence of adverse safety outcomes in the following six months, such as motor vehicle crashes, near-miss crashes, occupational exposures, and medical errors (Weaver et al. 2018).

Health professionals. Recent data from Canada, with reference to the year 2011, show that approximately 1.8 million Canadians (12% of the working population), were exposed to night shift work, and 45% were female. By occupation, professional occupations in health ranked second place (35% of workers), following occupations in protective services (37%) (Rydz et al. 2020). However, despite these numbers, and even if nurses and midwives make up almost 50% of the global healthcare shift working workforce, much of the research addressed to the shift work area used men (Matheson et al. 2019). Female nurses working in rotating night shift were found to have significantly lower mean scores in job satisfaction, sleep, and psychological well-being as compared to day shift workers (Verma et al. 2018) and even impaired sexual self-efficacy and sexual quality of life (Khastar et al. 2020). There is an extreme paucity of studies conducted on midwives,

although they play an important role in medical care: a systematic review of sleep-related/fatigue-management including more than 8600 participants, 89% females, did not find studies conducted in midwives (Querstret et al. 2020). In the same year, a survey study by the American College of Nurse-Midwives Sleep and Safety Taskforce, conducted on more than 4350 certified nurse-midwives and midwives to identify sleepiness, found that midwives working shifts >12 h had higher rates of excessive daytime sleepiness compared with those who worked shifts of ≤12 h (Arbour et al. 2019).

III. JUSTIFICATION

In the section "*State of the art*" previously exposed, in such a broad and detailed way, it has been highlighted how circadian rhythms greatly interfere with different states of health and disease.

In the case of obstetric care carried out by midwives, care that can be perfectly framed in the nurse meta-paradigm. Meta-paradigm that establishes the interrelation between the four concepts: person, health, environment and care.

The interference of circadian rhythms is equally present, both in the person, and in the environment that surrounds them, as professionals who perform their functions, in this case obstetric ones, and finally in the expected result, the awareness of state of health.

All this process led to the thesis work that is now presented, focusing both on professionals, midwives, and on an activity that is typical of this professional, such as childbirth care; understanding that the final result arises from the interrelation of all the factors mentioned.

Below we proceed to describe two studies that analyze the interrelation of chronobiology in the professional activity of the midwife, which has been defined as "*Chronobiological perspective in the midwifery profession: Self-awareness and professional care*"; breaking it down into A. Chronobiology and professional self-knowledge, describing the study entitled: "*Individual Circadian Preference, Shift Work, and Risk of Medications Errors: A Cross-Sectional Web Survey among Italian Midwives*", carried out by *Rosaria Cappadona, Emanuele Di Simone, Alfredo De Giorgi, Benedetta Boari, Marco Di Muzio, Pantaleo Greco, Roberto Manfredini, María Aurora Rodríguez-Borrego, Fabio Fabbian and Pablo Jesús López Soto*; and B. Chronobiology and professional care, showing the evidence obtained in study entitled: "*Daylight Saving Time and Spontaneous Deliveries: A Case-Control Study in Italy"*, in which authorship was *Rosaria Cappadona, Sara Puzzarini, Vanessa Farinelli, Piergiorgio Iannone, Alfredo De Giorgi, Emanuele Di Simone, Roberto Manfredini, Rosita Verteramo, Pantaleo Greco, María Aurora Rodríguez-Borrego, Fabio Fabbian and Pablo Jesús López Soto.*

IV. OBJECTIVES

1. GENERAL OBJECTIVE

a) Organization of circadian rhtyhms. To assess (by means of validated questionnaires via social media) individual circadian preference (chronotype), effects on sleep and perceived quality of life on nurses and midwives in collaboration with the Board of Nursing and Midwifery.

b) Desynchronization of circadian rhythms: daylight saving time and shiftwork. To study possible implications in nursing and midwifery-related aspects in health and disease conditions.

2. SPECIFICS OBJECTIVES

A.

- To assess individual circadian preferences, effects on sleep and perceived quality of life on midwives

- To determine the effect of chronotype and shift work in professional self-knowledge

B.

- To assess the association between the bi-annual change of daylight saving time and number of spontenous deliveries in a single Italian region.

- To determine the effect of daylight saving time in professional care.

V. CHRONOBIOLOGICAL PERSPECTIVE IN THE MIDWIFERY PROFESSION: PROFESSIONAL SELF-KNOWLEDGE AND CARE

A. CHRONOBIOLOGY AND SELF-KNOWLEDGE

1. RELATIONSHIP BETWEEN CHRONOTYPE, SHIFT WORK, AND RISK OF MEDICATION ERRORS AMONG ITALIAN MIDWIVES (CAPPADONA ET AL. 2020a)

1.1. Expected results

Based on the evidence provided in the "state of the art" section, we evaluated whether DST might affect the number of spontaneous deliveries in a single Italian region.

1.2. Material and methods

1.2.1. Study design and setting

A cross-sectional study through a prospective survey was carried out in midwifery profesionnals that belong to Italian Board of Nursing and Midwifery.

1.2.2. Participants, Ethical considerations, Procedures and Period

A sample of Italian midwives willing to participate in the survey were invited through the most frequently used social media, i.e., Facebook and Instagram, to complete a questionnaire. We chose this extremely smart method in order to maximize the final sample size and the willingness to fill a self-administered web survey allowed us to obtain the informed consent to take part in the survey, Thus, participation was voluntary and confidential.

The study obtained a favorable report from the Ethical Committee for Research with Humans of the University of Córdoba. There is also authorization from the Regional Coordination of the Order of the Midwife Profession of the Emilia Romagna Region for the development of the study (Prot.11/2019).

Midwifes were reached through social media, and those willing to fill the questionnaire were enrolled. In this case, they were told that their personal data would not have been recorded in any way; however, we asked them to declare their job activity, and we trusted health care professionals declaring to be midwifes at the time of starting the questionnaire. We could not analyse any other data nor the reason for refusing or agreeing to participate. All cases of incomplete questionnaire were excluded from the analysis.

The survey was built on Google Forms, and sent to Italian midwifes. Data was collected starting from 14 June 2019 to 31 August 2019. The statistical power of the sample to obtain statistically significant results was determined by a freely available on-line web platform. The authors

considered the appropriate sample size for an adequate study power considering a confidence level of 99% and a confidence interval of 5% on a total of about 21,000 midwifes working in Italy. The analysis computed a representative sample size of 377 midwifes. The confidence interval also called margin of error is the plus-or-minus figure usually reported in opinion poll results, whilst the confidence level suggests the level of security in excluding wrong answers.

1.2.3. Variables and Instruments

The questionnaire consisted of a cover page (describing the purpose of the study, as well the methods to ensure anonymity and voluntary participation), and three special sections, including several different items each. In particular, the special sections dealt with:

B. demography, actual working schedule, and working experience information;
C. the Morningness–Eveningness Questionnaire (MEQ), consisting of 19 questions about personal daily sleep-wake habits and the times of day of preference of certain activities, with assigned points from 0 to 5, giving a possible overall score ranging from 16 to 86. Five categories can be identified: definitely E-type (16–30), moderately E-type (31–41), neither type or I-type (42–58), moderately M-type (59–69), and definitely M-type (70–86). For ease of interpretation, we considered moderately E-type as E-type (16–41 points) and moderately M-type as M-type (59–86 points). Thus, we had three final subgroups: E-types, I-types, and M-types.
D. a perception of risk of medication errors survey, based on the "seven rights" (7R) rule of medication administration (right medication, right client, right dose, right time, right route, right reason, and right documentation) (Smeulers et al. 2015). As for risk evaluation, we chose "near misses", i.e., accidents that do not cause the patient harm (Kessels-Habraken et al. 2010), since they represent the majority of medication errors (Aseeri et al. 2020). The perception of risk of medication errors was evaluated on the basis of the following questions:
    a. Based on the 7R rule, during the last shift, how many times did you (or any of your colleagues) run the risk of making a medication error?
    b. Why medication error was about to occur?

1.2.4. Statistical analysis

For statistical analysis, first a descriptive analysis was performed, including results derived from either MEQ calculated score or personal self-perceived chronotype. The sample was classified

according to the self-perception of risk of medication errors, and subgroups by age, working schedule, years of working experience, and chronotype were then compared. Second, a logistic regression analysis was done, considering the self-perception of risk of medication errors as the dependent variable and all the other parameters as the independent ones. Third, a cluster analysis was performed, to determine the phenotype of health care professionals exposed to risk of medication errors based on demography, type of work, and chronotype. IBM Statistical Package for Social Science (SPSS 13.0 for Windows, SPSS Inc., Chicago, IL, USA) was utilized.

1.3. Results

The final sample included 401 Italian midwives (98.8% women), and the main characteristics are summarized in Table 2.

Table 2. Characteristics of the whole population of midwifes.

Number of participants (*n*)	**401**
Female (*n* (%))	396 (98.8)
Mean age (years)	38.5 ± 10.1
age 23–30 years (*n* (%))	102 (25.5)
age 31–35 years (*n* (%))	81 (20.0)
age 36–40 years (*n* (%))	79 (19.8)
age 41–45 years (*n* (%))	37 (9.2)
age 46–50 years (*n* (%))	37 (9.2)
age 51–55 years (*n* (%))	30 (7.5)
age 56–60 years (*n* (%))	35 (8.8)
University degree (*n* (%))	32 (8)
High school degree (*n* (%))	369 (92)
Shift work schedule (*n* (%))	293 (73)
Mean working experience (years)	11.7 ± 8.9

1.3.1. Chronotype, shift work and risk of medication errors

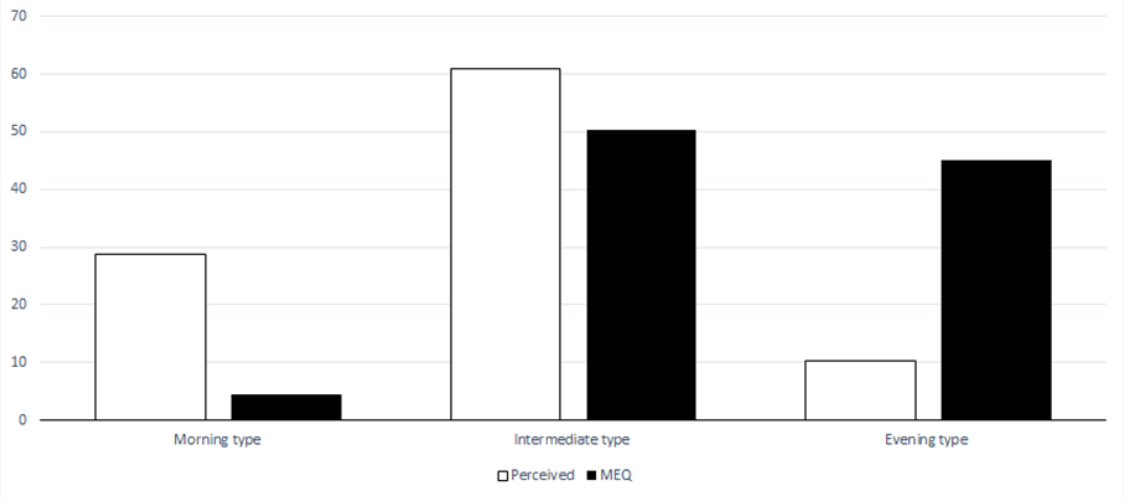
As for individual chronotype (MEQ score) and age, subgroups were represented as follows: age 23–30 years: 52±8.3; age 31–35 years: 56 ± 8.2; age 36–40 years: 58.2±7.6; age 4–45 years: 58.7±9.2; age 46–50 years: 60.5±8.3; age 51–55 years: 60.4±8; age 56–60 years: 58.5 ± 8.2 ($p<0.001$).

As for individual chronotype (self-perceived), subgroups were represented as follows: M-type n=115 (28.7%), I-type n=245 (61%), E-type: n=41 (10.2%). Mean MEQ score in groups who perceived M-type, I-type, and E-type was 64.8±5.1, 54.2±5.1, and 44.7±7.1, respectively (p<0.001).

As for individual chronotype (MEQ calculated score), subgroups were represented as follows: definite M-type: n=25 (6.3%); moderately M-type: n=156 (39%); I-type: n=202 (50.3%); moderately E-type: n=16 (4%); definite E-type: n= 2 (0.4%).

Graph 1 reports the distribution of groups by self-perceived and calculated chronotype. For ease of comparison, the MEQ calculated score was reported considering moderately E-type plus definite E-type as E-type and moderately M-type plus definite M-type as M-type.

Graphic 1. *Self-perceived and calculated chronotype distribution of groups.*

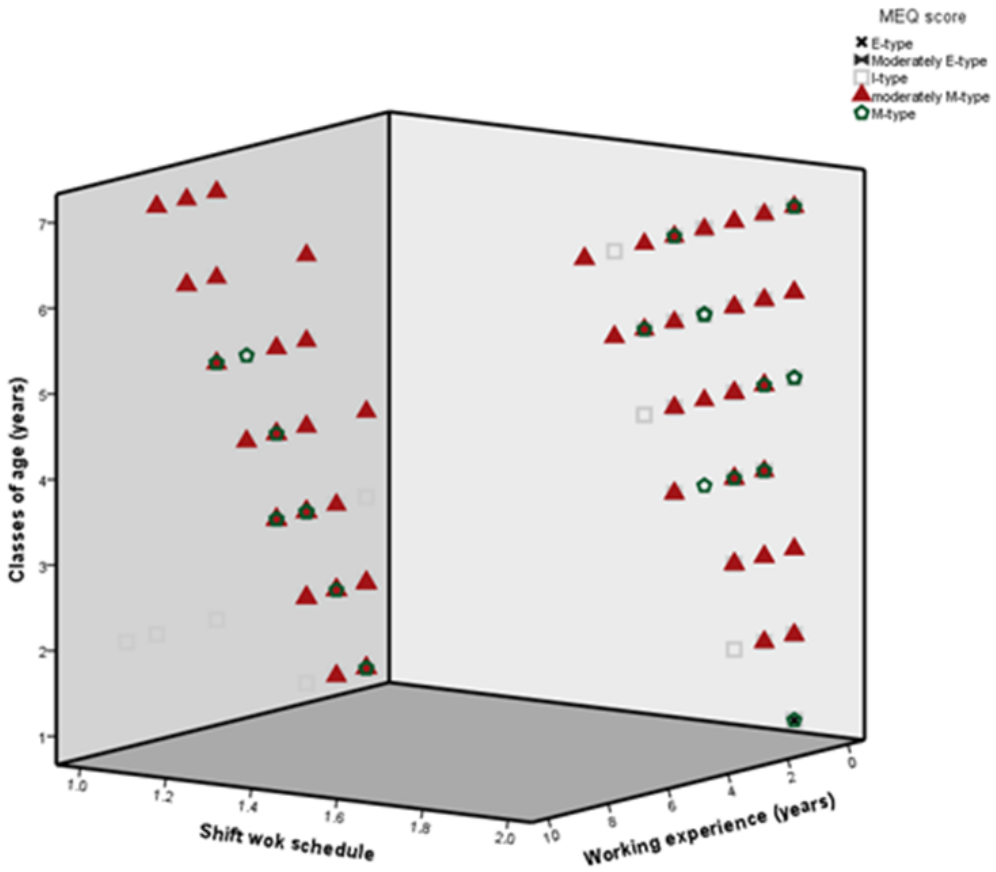


Note: For ease of comparison, the Morningness–Eveningness Questionnaire (MEQ) calculated score was reported considering moderately E-type plus definite E-type as E-type and moderately M-type plus definite M-type as M-type.

As for perception of risk of medication errors, subjects with response "no, never" were 208 (51.9%), and subjects with response "yes, at least once" were 193 (48.1%). The MEQ score did not show significant differences between the two groups (56.7±8.4 vs. 56.5±8.9, p=NS). No differences between the two groups were found for subgroups by class of age, working shift, years of working experience, and chronotype either.

Logistic regression analysis did not show any independent association with perception of risk of medication errors, whereas cluster analysis showed that perception of risk of medication errors was associated with class of age 31–35 years, shift work schedule, working experience 6–10 years, and I-type MEQ score. No perception of risk of medication errors was associated with age 46–50 years, daytime working, working experience 21–25 years, or M-type MEQ score (Figure 5).

Figure 4. *Cluster analysis relating age, shift work schedule, working experience, and MEQ score*



1.4. Discussion

The results of this study, addressed to investigate the possible relationship between chronotype and risk of medication errors in midwives, showed that the risk of medication errors was associated with younger age, shift work, relatively low working experience, and being an Intermediate chronotype. This is the first report on the association of shift work and risk medical errors in midwives. A recent multicentre Chinese study showed that sleep quality, social support, job satisfaction, occupational injuries, adverse life events, frequency of irregular meals, and employment type were statistically significant factors influencing fatigue among midwives (Chen et al. 2020). We found that younger persons, with reduced working experiences, were more likely to report an increased risk of error. It is possible that experience may help in attenuating the decrease in performance during night shift.

Errors. Medication error incidents are more likely to be reported in the morning shift (Aseeri et al. 2020; Suclupe et al. 2020), but it is common practice that morning therapy is prearranged by the night nursing crew at the end of their shift. Rhythm desynchronization exhibits also gender-specific differences (Cappadona et al. 2020), and studies on the circadian and sleep-wake-dependent

regulation of cognition in a forced desynchronization protocol showed that accuracy exhibited the largest sex difference in circadian modulation, with the worse performance in women in the early morning hours (at around 6 a.m.) (Santhi et al. 2016). Even risk taking, a complex form of decision-making that involves calculated assessments of potential costs and rewards, may play a role in the determination of errors. Both gender-specific and chronotype differences exist, since males report higher propensity for risk-taking, in particular E-types. However, although there is no significant difference in risk propensity or risk-taking behaviour across chronotypes in males, E-type females significantly report and take more risk than other chronotypes (Gowen et al. 2019).

Chronotype. Chronotype is also strongly implicated in performance tasks, also making reference to the so-called "synchrony effects", i.e., superior performance at optimal and inferior performance at suboptimal times of day. A study aimed at evaluating the effect of individual differences in chronotype on performance task, evaluated a sample of M-type and E-type women during a driving session in morning (8 a.m.) and evening (8 p.m.). A vigilance decrement was found when E-type participants drove at their nonoptimal time of day (morning session). In contrast, driving performance in the M-type group remained stable over time on task and was not affected by time of day (Correa et al. 2014). By contrast, studies on subjects tested for mean reaction times, error rates, and efficiency of three attentional networks (alerting, orienting, and executive control/conflict) at two time points (time 1 or baseline at 8 a.m.; time 2, after 18-h sustained wakefulness at 2 a.m.), showed that E-types participants outperformed M-types on incongruent time, i.e., deep night (Barclay & Myachykov, 2017). On one hand, negative effects of sleep impairments seem to be confirmed to affect more E-types than other chronotypes. An Australian online survey study conducted on paramedics (age 39 ± 12 years; 54% women; 85% rotating shift-workers; 57% I-types, 32% M-types, 11% E-types), showed significantly higher depression scores, anxiety, poorer sleep quality, and reduced general well-being in the E-types, compared with M-types (Khan et al. 2020). Our study identifies Intermediate-type as the group at higher risk of error. On one hand, this result is contradictory with respect to the available literature. On the other hand, this result, if confirmed, is extremely interesting since Intermediate chronotype represents the most frequent circadian preference and not only in our sample. Thus, the finding that younger midwives, with relatively limited working experience, and even with chronotype extremes, are exposed to higher risk of error during their night shift, raises serious concern.

Limitations. We are aware of several limitations to this study: (a) cross-sectional design, based on data collected through a web survey, therefore the sample could be sized only by social media users only; (b) the MEQ score, even if used in the majority of studies for assessing morningness–

eveningness preference, does not categorize for different ages (Levandoski et al. 2013); (c) to evaluate the risk of medication error, we considered the general definition of near misses. Although it is largely the most frequent incident reported, we did not differentiate between near misses and no harm incidents (Sheikhtaheri et al. 2014); (d) individual perception of the risk of medication errors is not a validated item yet; I logistic regression analysis did not identify independent factors; (f) we could not evaluate any gender effect, as most of the sample were women, as usually occurs for studies on nurses and midwives. However, there are also some positive aspects: (a) the web survey method warranted speed, and even in a short timeframe all different classes of age were represented; (b) we found that perception of chronotype was different from the effective profile identified by a well-validated score. This concept could help for future studies and also for practical applications since when workers (health care personnel in particular) ask for health measures, they very often make reference to personal perception.

Coping strategies. Midwifery and nursing are acknowledged as stressful occupations, and the negative impact of high stress levels often requires coping strategies. Of these, the eleven most used have been identified via interview material: drinking alcohol, smoking, using the staff social club, using social networking websites, exercising, family activities, home-based activities, outdoor activities, avoiding people, displacement, and sleep (Happell et al. 2013). Unfortunately, it is evident that some of these coping strategies are unhealthy and extremely concerning. Moreover, due to the stress burden, absenteeism is becoming a significant global problem, and taking a “mental health day” as sickness absence is a common phenomenon, taken by more than one half of nurses and midwives, according to an online cross-sectional survey in Australia (Lamont et al. 2017).

B. CHRONOBIOLOGY AND PROFESSIONAL CARE

2. DAYLIGHT SAVING TIME AND SPONTANEOUS DELIVERIES (CAPPADONA ET AL. 2020b)

2.1. Expected results

The aim of this study was to evaluate the possible association between chronotype, shift work, and risk of medication errors in midwives, inviting a representative sample of these health care professionals through a web survey. Social media, in fact, has increased the popularity since it represents a convenient method for communicating on the Web, for recruiting participants for health research, and for conducting survey studies by questionnaires [McCarthy & Mazza, 2019; Shaver, 2019].

2.2. Material and Methods

2.2.1. Study desing, Setting and Period

In this approach, a retrospective case-control study using administrative database was carried out. The Certificate of Childbirth Assistance (CedAP) was used to collect data from one single Italian region, Emilia-Romagna, in the period 2016–2018.

2.2.2. Participants

A cohort of 7415 deliveries registered from low-risk pregnancies with spontaneous onset of labor was enrolled in this case–control study. We identified the exact dates of DST during each year analyzed (Figure 5). Age and gestational age were evaluated. We defined the 2 weeks after DST as the exposure period and the 2 weeks before DST as the control period. Exclusion criteria are shown in Table 3.

Table 3. *Exclusion criteria applied on the sample.*

Exclusion criteria	
Not low risk pregnancy	Medically Assisted Procreation (MAP) pregnancies
Not cephalic presentation	Fetal anomalies
Induction of labor	Stillbirth
Multiple pregnancy	Elective Cesarean section
Fetal growth defects	

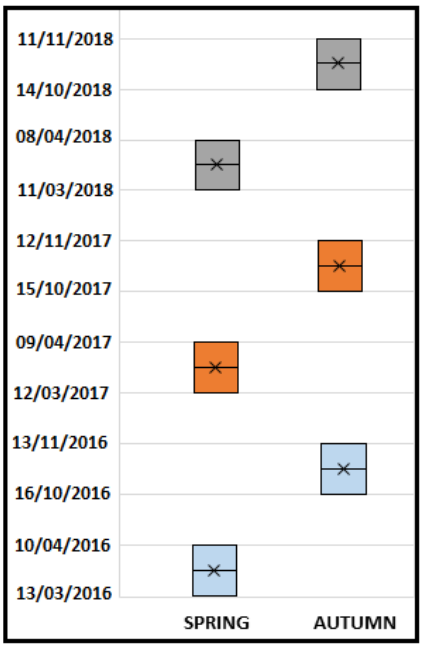


Figure 5. *The two weeks belonging to the control period and the exposure period identified by daylight saving time (DST) during each year analyzed (2016–2018) are reported (grey is related with 2016, orange with 2017 and light blue with 2018).*

2.2.3. Variables, Instruments and Statistical analysis

The primary outcome was defined as the number of deliveries, in particular the number of non-operative vaginal deliveries.

The rationale underlying the choice of the latter outcome was to exclude, as far as possible, the conditioning acted out by the health workers and the healthcare organizational system that weighs on the birth path, in order to bring out the influences that the endocrine and central nervous systems have on childbirth.

Secondary outcomes were:

- Gestational age at delivery, defining preterm before 37 weeks, at term between 37 and 41 weeks, and post term beyond 41 weeks;
- Type of delivery: vaginal delivery, caesarean section, or operative delivery;
- Time of delivery: time when the birth occurred, combining three moments of the day-morning (08:00–15:59), afternoon (16:00–23:59), or night (00:00–07:59);
- Birth weight, divided into three distinct classes: less than 2500g, between 2500 and 4000g, and more than 4000g;
- Five-minute Apgar at birth;
- Use of analgesia in labor.

We also analyzed local data relating to individual provinces. In particular, the number of at term deliveries that occurred in the three-year period was considered in the various Emilia-Romagna provinces, in order to verify whether there were any differences related to DST. The statistical analysis of the data was performed with the "chi-square" test. We considered a 5% error with a confidence interval of 95%, standard deviation of 0.5, and z-score of 1.96. The differences in the number of deliveries across the Spring and Autumn shifts were assessed for significance using the Poisson Means Test.

Annual birth rate was calculated as the ratio between the number of births during the two weeks pre- and post-DST, and the mean value of births obtained by the sum of births in the previous and the considered year divided by 2. The ratio was then multiplied by 103. This calculation was performed for any year considered in this study (Graph 2).

$$N\ (x) = \frac{\mathrm{N(x)}}{\left[\frac{\mathrm{B(x-1)}}{2} + \frac{\mathrm{B(x)}}{2}\right]} * 1000$$

N = number of births during the index 2 weeks;

X = year considered; x−1 = previous year;

B = total births in the Emilia-Romagna region of Italy.

Graphic 2. *Formula used to calculate the number of deliveries during the index 2 weeks.*

In addition, we calculated the age and gestational age of participants. A logistic regression analysis was carried out, where the period including the two weeks pre- and post-DST was the dependent variable and the other parameters investigated in this study the independent ones. A 2-sided p-value <0.05 was considered statistically significant. IBM Statistical Package for Social Science (SPSS 13.0 for Windows, SPSS Inc., Chicago, IL, USA) was used.

2.3. Results

The mean age of the 7415 women was 31.4±5 years, and mean gestational age was 39.3±1.4 weeks. Italian patients were 4801 (64.7%), whilst 35.3% were classified as non-Italian. The mean age of the women who delivered during the two weeks before DST were older than those who delivered during the two weeks post DST (31.6±5.4 vs. 31.3±5.3 years, p=0.033); on the contrary, gestational age was not different in the two groups (39.3±1.4 vs. 39.3±1.4 weeks, p=ns). As regarding time of delivery, 2708 births occurred in the morning (36.5%), 2022 (27.3%) in the afternoon, and 2685 (36.2%) at night. Birth rate during the Spring and Autumn shifts in the three different years of the study are shown in Table 4.

Table 4. *Birth rates in the years 2016, 2017, and 2018 are shown.*

Year of study	**Spring shift**		**Autumn shift**	
	Control period	Exposure period	Control period	Exposure period
2016	18.39	17.42	20.89	21.21
2017	17.52	14.04	19.03	19.00
2018	16.27	17.99	17.03	17.12

Data are expressed as * $10^{3.}$

2.3.1. Primary Outcome

Our results showed a difference in the number of deliveries between the exposed and the control groups, although it did not reach statistical significance (Table 5).

No statistical difference has been observed in the analysis of the number of deliveries (p=0.46), including mode of delivery (vaginal delivery, caesarean section, or operative delivery) and gestational age (term, preterm, post term). The same result was obtained analyzing the number of spontaneous deliveries (p=0.73).

***Table 5**. Summarized data of results of primary outcome.*

Primary Outcome	**Spring shift**		**Autumn shift**		**Chi-square**	***p*-Value (α = 5%)**
	Control period	Exposure period	Control period	Exposure period		
Number of deliveries	1781	1727	1950	1957	0.546	0.46
Number of spontaneous deliveries	1588	1536	1744	1716	0.120	0.73

The differences in the number of deliveries and number of spontaneous deliveries across the Spring and Autumn shifts assessed by the Poisson Means Test were not significant (p=0.37, p=0.92, p=0.6, and p=0.65 respectively).

2.3.2. Secondary Outcome

There were no significant differences in the secondary outcomes analyzed, between what was detected during the exposure period and what was found in the control period (Table 6).

***Table 6**. Summarized data of results of secondary outcomes (1/2)*

Secondary Outcome	**Spring shift**		**Autumn shift**		**Chi-square**	***p*-value (α = 5%)**
	Control period	Exposure period	Control period	Exposure period		
Delivery at term	1700	1652	1860	1849	0.227	0.63
Vaginal delivery at term	1516	1468	1663	1623	0.024	0.89
Post-term delivery	22	14	18	26	2.474	0.12
Preterm delivery	52	55	65	74	0.082	0.78
Type of delivery						
Cesarean Section	103	83	104	119	3.099	0.08
Operative delivery	90	108	102	122	0.0003	0.99

Table 6. *Summarized data of results of secondary outcomes (2/2)*

Time of delivery						
Morning (5:01 a.m. to 1:00 p.m.)	605	605	667	674	0.017	0.89
Afternoon (1:01 p.m. to 9:00 p.m.)	526	506	600	585	0.025	0.87
night (9:01 p.m. to 5:00 a.m.)	650	615	681	696	0.980	0.32
Birth weight						
Less than 2500 g	30	28	43	43	0.001	0.97
Between 2500 and 4000 g	1625	1579	1771	1785	0.564	0.45
More than 4000 g	126	120	136	129	0.0005	0.98
5-min Apgar at birth						
Apgar 7 at 5 min	11	6	10	12	0.760	0.38
Apgar 8 at 5 min	22	29	28	36	0.015	0.90
Apgar 9 at 5 min	242	245	270	254	0.339	0.56
Apgar 10 at 5 min	1502	1441	1632	1643	0.899	0.34
Use of analgesia in labor	313	299	355	357	0.217	0.64

Women's age was independently associated with delivery during the two weeks post DST (OR 1.010, 95% Confidence intervals 1.002–1.019, p = 0.021). All the other investigated parameters were not associated with the period of the DST. Therefore, every year of increasing age of the delivering woman increased the risk of event occurrence during the two weeks after DST of 1.0% (Table 7).

Table 7. *Logistic regression analysis considering the period including the two weeks pre- and post-DST as the dependent variable and the other parameters investigated the independent ones.*

Variables	**Odds Ratios**	**95% Confidence intervals**	***p***
Maternal age	1.010	1.002–1.019	0.021
Gestational age	1.005	0.970–1.041	0.801
Type of delivery	0.917	0.780–1.079	0.295
Time of delivery	1.044	0.930–1.172	0.466
Birth weight	1.000	1.000–1.000	0.639
5-min Apgar at birth	1.025	0.947–1.109	0.545
Use of analgesia in labor	1.023	0.900–1.163	0.726

Finally, we assessed the percentages of type and time of delivery during the Spring and Autumn shifts, but we could not find any difference.

2.4. Discussion

The present study found no statistically significant differences in the number of deliveries that occurred during the two weeks following DST compared to those occurring prior to the DST shifts. The same result was obtained for each secondary outcome analyzed. These data confirm the findings by Laszlo (2016) also for the latitudes and climatic conditions of the Emilia-Romagna region of Italy, despite the difference in daily average hours of sunlight (approximately 180 and 50 monthly sun-hours in March and October, respectively, in Sweden, vs. 190 and 100 in March and October, respectively, in Italy). The Swedish study, in fact, showed that the number of daily and weekly deliveries in the case and control group was similar, and statistically significant (IR 1.005, 95% CI 0.990–1.019), underlining the validity of the result only for latitudes, exposure to light, and climatic conditions to which the people included in the sample are subjected. Although the characteristics just stated for Sweden and the Emilia-Romagna region are extremely different, in both studies, it is confirmed that the transition from standard time to summertime and vice versa does not impact on the number of deliveries.

These results confirm data from Roizen (2007) regarding the role of oxytocin in the onset and completion of childbirth and its rhythmicity. Hormone secretion, in fact, has its own circadian rhythm, not influenced by the alternation of dark and light and, therefore, not affected by the change of time. This may explain why the number of deliveries in the two weeks following the transition from standard time to summertime, and vice versa, is almost superimposable to that found in the two weeks preceding it.

The analysis of type of delivery was based on the hypothesis of a possible influence of DST on the secretion of melatonin (Olcese et al. 2012; Sharkey & Olcese, 2007; Sharkey et al. 2009; Olcese & Beesley, 2014), through the indirect evaluation of the outcome of contractile activity. In this case, we could expect to observe a greater number of operative deliveries and caesarean sections in the weeks following DST shifts, caused by dynamic or mechanical dystocia induced by anomaly or stop of contractions. This difference was more marked in the Spring period as the transition from wintertime to summertime leads to the loss of one hour of darkness, with a consequent increase in light exposure and reduction in serum melatonin levels and, presumably, also in valid contractions. However, our data do not allow confirmation of this hypothesis; both the statistical analysis performed on the number of caesarean sections ($p=0.08$) and that relating to the operative deliveries ($p=0.99$) do not allow us to exclude that what has been detected is not attributable to simple chance.

Another relevant finding in the secondary outcome analysis was the confirmation of previous data collected in Texas, USA, by Mancuso (2004). In our sample also, relating to the Emilia-Romagna region, the transition from standard time to summertime does not significantly affect the time of delivery, regardless of the gestational period and the way it occurs.

Neonatal birth weight was also investigated as a secondary outcome, to test the hypothesis of a short-term, acute effect of rhythm disruption. This is because the available data in the literature refer to studies performed on shift worker women (Lin et al. 2011), and shift work represents a chronic, long-term condition of rhythm desynchronizing effect. According to this hypothesis, the expected result could be, therefore, an increase in newborns with a low birth weight (<2500g) in the weeks following the time change. However, the data obtained allow us to affirm that the transition from solar time to summertime and vice versa does not have a statistically significant effect on the increase in the incidence of newborns born with a low birth weight (<2500g) (p=0.97). It is possible to extend the same statement to the other investigated weight classes (2500–4000g: p-value=0.45; >4000g: p=0.98). Thus, we can conclude that DST shift does not have a statistically significant impact on newborn birth weight.

The rationale for the analysis of the use of epidural analgesia in periods of exposure and control was to assess whether the desynchronization induced by DST that shifts the transition could play a role in the perception of pain. In this case also, the results obtained do not allow us to exclude that the differences found are attributable to chance (p=0.64).

We took into consideration age and gestational age of this low-risk population and we found that the mean age of women who delivered during the two weeks before DST was older than those who delivered during the two weeks post DST and that women's age was independently associated with delivery during the two weeks post DST. We do not think that these findings could be of any relevant clinical significance due to the very small difference in age between the two groups. Moreover, these results could be related to the selection criteria aiming at evaluating only very low risk pregnancies.

We are aware of several limitations: (i) retrospective observational study; (ii) lack of perinatal complications—however, we selected only very low risk pregnancies; (iii) three years represent a short period of observation; (iv) unfortunately, we did not apply the methods used by László (2016) due to the different statistical package used for analysis—in fact, we used SPSS instead of SAS. Finally, (v) possible differences by race and ethnicity, since 35% of patients were not Italian. However, according to the last report of the Ministry for Health (year 2017) (Ministero della Salute, 2017), in Italy, 21% of the births were related to mothers of non-Italian citizenship. This

phenomenon is more widespread in the areas of the country with a greater foreign presence, i.e., in the Center–North, where more than 25% of births are from non-Italian mothers; in particular, in Emilia-Romagna and Lombardy, approximately 31% of births refer to foreign mothers. The most represented geographical areas of origin are Africa (27.7%), European Union (24.4%), Asia (18.1%), and South America (7.5%) (Ministero della Salute, 2020).

However, the present study has also several strengths: (i) the large sample size, (ii) the quality of the data, and (iii) the rigorous methodology. The sample analyzed is representative of women characterized by a very low risk pregnancy, and the Emilia-Romagna region is characterized by one the best regional health systems in Italy. The choice of performing the study in a specific Italian region allowed us to obtain a reliable, good, complete, uniform, and coded source of data. The Childbirth Assistance Certificate is unique for the entire regional territory, and its compilation is mandatory following each birth in the region, independent of the structure in which it takes place.

VI. CONCLUSIONS

A. Chronobiology and professional self-knowledge

Younger midwives, with lower working experience, engaged in shift work and belonging to an Intermediate chronotype, seem to be at higher risk of potential medication error. At least to the best of our knowledge, this is the first web survey study addressed to the relationship between chronotype, shift work, and perceived risk of medication error in midwives. Since morning hours seem to represent highest risk frame for female healthcare workers and shift work is not always aligned with individual circadian preference, our preliminary reports could stimulate further specific research aimed to practical applications. For example, assessment of individual chronotype and sleep attitude in healthcare personnel, through validated questionnaires, just previously suggested in terms of prevention of metabolic diseases (Manfredini et al. 2019), could provide easy and inexpensive method to identify subjects at potential higher risk of circadian disruption. Again, possible countermeasures, such as time-scheduled naps during night-shifts, have been positively tested on female nurses, who showed significantly greater increments in performance between 3:00 and 7:00 a.m. on nap versus no-nap nights (Zion & Shochat, 2019). Last but not least, attention to shift work consequences, together with specific training programs, could help to reduce medication errors and improve patients' safety (Di Simone et al. 2018(.

B. Chronobiology and professional care

There are no differences in the number of deliveries in the weeks following the change of time compared to those that precede it, neither during the Spring nor in the Autumn. This finding provides further confirmation to previous data obtained at quite different conditions of latitude, climate, and light exposure. It is possible that the multihormonal etiology of labor may explain this phenomenon. It would be interesting to extend the study to different latitudes and ethnicities, in order to verify whether our findings could be generalized or not.

- **General**

Regarding the general conclusions, chronobiology seems to be crucial to better understand persons' behaviour, environment, health, and practice, the major milestones of the metaparadigm considering caring.

Results of both studies show that in midwives the chronotype and a chrono-disruptor of circadian rhythms such as shift work, influence professional self-perception, specifically the perception of risk of medication. On the other hand, the chronodisruption generated by DST does not seem to affect the incidence of spontaneous deliveries in a specific Italian area. Consequently, the professional care provided by the midwife does not appear to be altered by the bi-annual change.

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VIII. APPENDICES

APPENDIX I: Table A and B

Doctoral student: **Rosaria Cappadona**

Table A. Publications that the doctoral student has carried out in the year 2019 (Feb 21)-2020 (November 3) (1/4)

N°	Authors	Title	Journal, year	Rank Quartile (Q) Decile (D) ISI Branch	Impact factor ISI 2020
1	**Cappadona R**, Puzzarini S, Farinelli V, Iannone P, De Giorgi A, Di Simone E, Manfredini R, Verteramo R, Greco P, Rodríguez-Borrego MA, Fabbian F, López-Soto PJ	*Daylight Saving Time and Spontaneous Deliveries: A Case-Control Study in Italy*	Int J Environ Res Public Health. 2020 Nov 3;17:E8091	58/193 Q2 PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	2.849
1	Fabbian F, De Giorgi A, **Cappadona R**, Lamberti N, Manfredini F, Limido A, Postorino M, StorariA, Manfredini R.	*Infodemiology of renal diseases: a novel opportunity to investigate public global interest*	European Review for Medical and Pharmacological Sciences	106/270 Q2 PHARMACOLOGY & PHARMACY	3.024
2	Manfredini R, **Cappadona R**, Tiseo R, Bagnaresi I, Fabbian F.	*Light, circadian rhythms and health.*	Therapeutic Landscape Design.Methods, design strategies and new scientific approaches. Chapter in volume, Springer Briefs; *in press*	NA	NA Scopus
3	**Cappadona R**, De Giorgi A, Di Simone E, Zucchi B, Rodriguez Borrego MA, Lopez Soto PJ, Fabbian F, Manfredini R.	*Sleep, dreams, nightmares, and sex-related differences: a narrative review.*	Eur Rev Med Pharmacol Sci.; *in press*	106/270 Q2 PHARMACOLOGY & PHARMACY	3.024
4	**Cappadona R**, Di Simone E, De Giorgi A, Zucchi B, Fabbian F, Manfredini R.	*Biological rhythms, health and gender-specific differences.*	It J Gender-Specific Med.; *in press*	NA	NA Scopus
5	Flacco ME, Acuti Martellucci C, Bravi F, Parruti G, **Cappadona R**, Mascitelli A, Manfredini R, Mantovani L, Manzoli L.	*Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis.*	Heart. 2020 Oct;106(19):1519-1524.	25/138 Q1 CARDIAC & CARDIOVASCULAR SYSTEMS	5.213

Table A. Publications that the doctoral student has carried out in the year 2019 (Feb 21)-2020 (November 3) (2/4)

6	**Cappadona R**, Di Simone E, De Giorgi A, Boari B, Di Muzio M, Greco P, Manfredini R, Rodríguez-Borrego MA, Fabbian F, López-Soto PJ.	*Individual circadian preference, shift work, and risk of medication errors: a cross-sectional web survey among Italian midwives.*	Int J Environ Res Public Health. 2020 Aug 11;17(16):E5810.	58/193 Q2 PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	2.849
7	Di Simone E, Fabbian F, Giannetta N, Dionisi S, Renzi E, **Cappadona R**, Di Muzio M, Manfredini R.	*Risk of medication errors and nurses' quality of sleep: a national cross-sectional survey in Italy.*	Eur Rev Med Pharmacol Sci. 2020;24:7058-7062.	106/270 Q2 PHARMACOLOGY & PHARMACY	3.024
8	Dionisi S, Di Simone E, Franzoso V, Caldarola E, **Cappadona R**, Di Muzio F, Giannetta N, Di Muzio M.	*The application of the theory of planned bahaviour to prevent medication errors: a scoping review.*	Acta Biomed. 2020;91(6-S):28-37.	NA	NA Scopus
9	Acuti Martellucci C, Flacco ME, **Cappadona R**, Bravi F, Mantovani L, Manzoli L.	*SARS-CoV-2 pandemic: an overview.*	Adv Biol Regul. 2020:77:100736	NA	NA Scopus
10	Fabbian F, De Giorgi A, Di Simone E, **Cappadona R**, Lamberti N, Manfredini F, Boari B, Storari A, Manfredini R.	*Weekend effect and in-hospital mortality in elderly patients with acute kidney injury: a retrospective analysis of a national hospital database in Italy.*	J Clin Med. 2020;9:1815	36/165 Q1 MEDICINE, GENERAL & INTERNAL	3.303
11	De Giorgi A, Di Simone E, **Cappadona R**, Boari B, Savriè C, Gallerani M, Lopez-Soto PJ, Rodriguez-Borrego MA, Manfredini R, Fabbian F.	*Validation and comparison of a modified Elixhauser index for predicting in-hospital mortality in Italian internal medicine wards.*	Risk Manag Healthc Policy. 2020;13:443-451.	24/87 Q2 HEALTH POLICY & SERVICES	2.429
12	Messina MP, D'Angelo A, Battagliese G, Coriale G, Tarani L, Pichini S, Rasio D, Parlapiano G, Fiore M, Petrella C, Vitali M, Ferraguti G, Ceccanti M; FASD Study Group (Bertoli D, Canepa M, **Cappadona R**, D'Alessio A, Danza M, Morese A, Paolino A, Pileri F, Pinna N, Neri I, Razzano R, Ricci A, Rizzi M).	*Fetal alcohol spectrum disorders awareness in health professionals: implications for psychiatry.*	Riv Psichiatr. 2020 Mar-Apr;55(2):79-89.	130/155 Q4 PSYCHIATRY	1.184
13	Ricchi A, Prepelita T, Messina MP, **Cappadona R**, Molinazzi MT, Fieschi L, Nespoli A, Guana M, Cervi G, Parma D, Mauri PA, Artioli G, Banchelli F, Foa C, Neri I.	*Self-efficacy in breastfeeding support: a research on Italian midwifery students: Running head: Student's self-efficacy in breastfeeding support.*	Acta Biomedica. 2020;91:27-34.	NA	NA Scopus

Table A. Publications that the doctoral student has carried out in the year 2019 (Feb 21)-2020 (November 3) (3/4)

14	Fabbian F, Coppola A, **Cappadona R**, De Giorgi A, Fanaro S, Di Simone E, Manfredini R, Greco P, Rodriguez Borrego MA, Lopez Soto PJ.	*Ambulatory blood pressure monitoring during pregnancy: an Italian experience.*	Clin Exp Obstet Gynecol. 2020;47(1):89-92.	82/82 Q4 OBSTETRICS & GYNECOLOGY	0.139
15	Gabutti G, Carioli U, Gamberoni D, Masetti G, Matteo G, Perrone P, **Cappadona R**, Greco P, Siliquini R, Stefanati A.	*Use of information sources on vaccine-preventable diseases in pregnant women: an experience in Ferrara, Italy.*	Int J Environ Res Public Health. 2019 Dec 28;17(1). pii: E233.	58/193 Q2 PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	2.849
16	Vitagliano A, Andrisani A, Dessole F, Virdis G, **Cappadona R**, Marin L, Capobianco G, Dessole S, Ambrosini G.	*Rectovaginal endometriosis: head to head comparison between sonovaginography and magnetic resonance imaging.*	Clin Exp Obstet Gynecol. 2019;46(6):888-891	82/82 Q4 OBSTETRICS & GYNECOLOGY	0.139
17	Virdis G, Dessole F, Andrisani A, Vitagliano A, **Cappadona R**, Capobianco G, Cosmi E, Ambrosini G, Dessole S.	*Cesarean scar pregnancy: a report of three cases and a critical review on the management.*	Clin Exp Obstet Gynecol. 2019;46(6):982-985	82/82 Q4 OBSTETRICS & GYNECOLOGY	0.139
18	Dessole F, Virdis G, Andrisani A, Vitagliano A, **Cappadona R**, Dessole S, Cosmi E, Capobianco G, Ambrosini G.	*Fetal congenital cystic adenomatoid malformation (CCAM pathogenesis, and clinical management: a case report).*	Clin Exp Obstet Gynecol. 2019;46(6):999-1002	82/82 Q4 OBSTETRICS & GYNECOLOGY	0.139
19	Manfredini R, Fabbian F, De Giorgi A, **Cappadona R**, Capodaglio G, Fedeli U.	*Daylight saving time transitions and circulatory deaths: data from the Veneto region of Italy.*	Intern Emerg Med. 2019 Oct;14(7):1185-1187	59/165 Q2 MEDICINE, GENERAL & INTERNAL	2.322
20	Manfredini R, **Cappadona R**, Fabbian F.	*Is Takotsubo still a benign disease? Complications (and gender) make the difference.*	Angiology. 2019 Oct;70(9):795-796	39/65 Q3 PERIPHERAL VASCULAR DISEASE	2.255
21	Fabbian F, Savriè C, De Giorgi A, **Cappadona R**, Di Simone E, Boari B, Storari A, Gallerani M, Manfredini R.	*Acute Kidney Injury and In-Hospital Mortality: A Retrospective Analysis of a Nationwide Administrative Database of Elderly Subjects in Italy.*	J Clin Med. 2019 Sep 2;8(9). pii: E1371.	36/165 Q1 MEDICINE, GENERAL & INTERNAL	3.303

Table A. Publications that the doctoral student has carried out in the year 2019 (Feb 21)-2020 (November 3) (4/4)

22	Manfredini R, **Cappadona R**, Fabbian F.	*Heat stress and cardiovascular mortality in immigrant workers: can we do something more?*	Cardiology. 2019;143(1):49-51.	93/138 Q3 CARDIAC & CARDIOVASCULAR SYSTEMS	1.791
23	Manfredini R, **Cappadona R**, Fabbian F.	*Letter by Manfredini et al Regarding Article "Ambulance Density and Outcomes After Out-of-Hospital Cardiac Arrest: Insights from the Paris- Sudden Death Expertise Centre Registry"*	Circulation. 2019 Sep 9;140(10):e547-e548.	1/138 Q1 CARDIAC & CARDIOVASCULAR SYSTEMS	23.603
24	Andrisani A, Vitagliano A, Virdis G, Dessole F, **Cappadona R**, Marin L, Capobianco G, Dessole S, Ambrosini G.	*Accuracy of transvaginal ultrasound, saline infuzion sonohysterography, and office hysteroscopy in the diagnosis of endometrial polyps.*	Clin Exp Obstet Gynecol 2019;46(4):623-625	82/82 Q4 OBSTETRICS & GYNECOLOGY	0.139
25	Verteramo R, Picarelli V, Labianco S, Ismail SY, Iannone P, Indraccolo U, **Cappadona R**, Morano D, Martinello R, Greco P.	*Vaginal deliveries after cesarean section: heterogeneity of outcome according to the hospital policies in Italy.*	It J Gynaecol Obst 2019 March;31(1):7-13	NA	NA Scopus
26	Fabbian F, Tonelli L, De Giorgi A, **Cappadona R**, Pasin M, Manfredini R.	*Early prognostic value of nocturnal blood pressure: a single-centre experience.*	Blood Press Monit. 2019 Jun;24(3):120-122.	63/65 Q4 PERIPHERAL VASCULAR DISEASE	1.092
27	Lopez Soto PJ, Fabbian F, **Cappadona R**, Zucchi B, Manfredini F, Garcia Arcos A, Carmona Torres JM, Manfredini R, Rodriguez Borrego MA.	*Chronotype, nursing activity and gender: a systematic review.*	J Adv Nurs. 2019;75(4):734-748.	6/123 Q1 NURSING	2.561
28	Manfredini R, Fabbian F, **Cappadona R**, De Giorgi A, Bravi F, Carradori T, Flacco ME, Manzoli L.	*Daylight saving time and acute myocardial infarction: a meta-analysis.*	J Clin Med. 2019;8(3). pii: E404.	36/165 Q1 MEDICINE, GENERAL & INTERNAL	3.303
29	Manfredini R, **Cappadona R**, De Giorgi A, Fabbian F.	*To marry or not.*	Am J Cardiol. 2019;123(7):1185.	63/138 Q2 CARDIAC & CARDIOVASCULAR SYSTEMS	2.570
				Total	**70,219**

Table B. Conference presentations that the doctoral student has carried out in the year 2019-2020

N°	Authors	Conference, City, Date	Type	Title
1	**Cappadona R**, Coppola A, Greco P, Fabbian F, Manfredini R	World Congress on Gynecology & Women's Health, Dubai, UAE, June 17-18, 2019	Lecture	Ambulatory blood pressure monitoring during pregnancy.
2	Manfredini R, Fabbian F, **Cappadona R**, De Giorgi A, Flacco ME, Manzoli L.	18th European Congress of Internal Medicine, Lisbon, Portugal, August 29-31, 2019	Poster	Daylight saving time transitions and acute myocardial infarction: a meta-analysis of the available evidence.
3	Manfredini R, **Cappadona R**, Fabbian F, De Giorgi A, Capodaglio G, Fedeli U.	18th European Congress of Internal Medicine, Lisbon, Portugal, August 29-31, 2019	Poster	Daylight saving time transitions and circulatory deaths: a study in the Veneto region of Italy.
4	Manfredini R, **Cappadona R**, Tiseo R, Fabbian F, De Giorgi A, Capodaglio G, Fedeli U.	IGM Congress 2019, 9th Congress of the International Society of Gender Medicine, Vienna, Austria, September 12-13, 2019	Poster	Daylight saving time and circulatory deaths: are there differences by sex? Data from the Veneto region of Italy.
5	**Cappadona R**, Capucci R, Paganelli C, Rizzati M, Fabbian F, Manfredini R, Greco P, Rodriguez Borrego MA, Lopez Soto PJ.	IGM Congress 2019, 9th Congress of the International Society of Gender Medicine, Vienna, Austria, September 12-13, 2019	Poster	Gender violence: a study of awareness implementation at the University Hospital of Ferrara, Italy.
6	Manfredini R, Boari B, Savriè C, **Cappadona R**, Tiseo R, De Giorgi A, Fabbian F, Capodaglio G, Fedeli U.	120° National Congress of the Italian Society of Internal Medicine, Rome, Italy, October 18-20, 2019	Poster	Daylight saving time, circulatory deaths, and age: data from the Veneto region of Italy.
7	Manzoli L, Flacco ME, Bravi F, Carradori T, **Cappadona R**, Fabbian F, De Giorgi A, Manfredini R.	12th European Public Health Conference, Marseille (FRA), November 20-23, 2019	Poster	Daylight saving time and acute myocardial infarction: a meta-analysis.
8	Manfredini R, **Cappadona R**, Savriè C, Boari B, Tiseo R, Bagnaresi I, De Giorgi A, Fabbian F, Capodaglio G, Fedeli U.	80° National Congress of the Italian Society of Cardiology, Rome, Italy, December 12-15, 2019	Poster	Deaths from ischemic heart diseases and daylight saving time transitions: a retrospective analysis in the Veneto region of Italy.
9	**Cappadona R**, Di Simone E, De Giorgi A, Boari B, Di Muzio M, Greco P, Manfredini R, Rodríguez-Borrego MA, Fabbian F, López-Soto PJ.	XI Jornadas de Jóvenes Investigadores del IMIBIC, Cordoba, Spain, October 29-30, 2020	Poster	Chronotype, shift work and risk of medication errors in Italian midwives.