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# Adult patients with *grown-up congenital heart* disease: lights and shadows

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## ABSTRACT

GUCH is acronym of *grown-up congenital heart* of patients who become adults after cardiac surgery. The history of this population is in progress (temporal perspective), and long-term post-surgical follow-up revealed the paradoxical meaning of *correction of complex congenital heart disease*, because surgery does not restore normality: it prolongs life, improves symptoms, functional capacity, but it is often associated with illness and peculiar needs. Not only survival but also health-related quality of life, which is strictly connected to clinical status, socio-economic situation, psychological conditions, cognitive functions, level of care with particular attention to gender differences. Currently the history of these patients is better known: a multidisciplinary team of cardiologists with specific training in congenital heart disease, psychologists, neurophysiologists, obstetricians, social workers, experts in human science can improve the possibilities of these patients to realize their effective and safe project of life.

## Introduction

More than 60 years have passed since Lillehei *The father of open surgery* started the era of correction of congenital heart diseases.[1] At the end of the sixties, only the minority of patients with complex congenital heart diseases survived the first year after birth;[2] nowadays on the contrary, the grown-up congenital heart population exceeds the pediatric one.[3-5] The reasons for such a change are different: fetal echocardiography has made prenatal diagnosis of heart anomalies possible, thus causing the raise of interruptions of pregnancy. On the other hand, the high diagnostical accuracy and the brilliant surgery outcome along with an improved medical management allow higher survival rates.[6-8] In the early seventies Perloff foretold: *...it is a simple matter of time before a population of adults with congenital heart disease would emerge [...]; we are obliged to look beyond the present and define our ultimate goal: the quality of life of long-term survival*.[9]

If the surgical result is easily quantified by two simple conditions - death *versus* survival -, definition of late outcome is more complex because of various determinants, related not only to native cardiac defect and its modifications after surgery, but bound fast to personal profile, evolutionary growth, psychological functioning, neurophysiological activities, interaction with the reality and capability to spend *normality*.[10]

During the past 50 years many updates have involved surgical techniques, timing of correction, protection of brain and heart during surgery, but the greatest changes have affected society, bringing raising needs and expectations.[11,12]

Long-term post-surgical follow-up has revealed the paradoxical meaning of *correction of complex congenital heart disease*. Heart surgery does not restore normality: it prolongs survival and improves symptoms and functional capacity, but it represents as well a source of illness.[13] Patients with complex congenital heart disease need medical or surgical interventions and re-interventions; moreover, the post-surgical history is different in patients treated with different surgical techniques.[14] Patients that underwent atrial switch surgery for transposition of the great arteries during the '60s and '70s, original Fontan's procedure for univentricular heart or palliative surgery for tetralogy of Fallot, have different clinical histories compared to patients operated during '80s and '90s for the same defects but with improved surgical techniques and approaches. First surgical procedures showed severe limitations in the long term, so arterial switch took over Mustard's and Senning's atrial switch,[15,16] total cavo-pulmonary connection replaced Fontan's procedure and its variations[17]

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(Figure 1), right ventricle manipulation, ventriculotomy and right ventricle outflow tract reconstruction were superseded by trans-pulmonary combined approach;[18,19] percutaneous interventions represent a valid alternative with reduced operatory risk for the management of post-surgical sequelae.[20] Electrophysiology techniques can treat complex arrythmias, that represent the major cause of sudden death and early worsening of ventricular function[21] (Figure 2). Anyway, even if younger patients benefit from these interventions, at present we do not know the long-term outcome. Our knowledge is temporary limited and follow-up duration is the major risk factor for old and new complications. At the end of '80s the Boston's group implemented early surgical correction for various complex congenital heart defects,[22,23] thus eliminating palliative surgery and leading to many advantages: the reduction of total number of interventions per patient reduced surgery-related mortality; the anticipation of correction suppressed illness caused by persistent low oxygen saturation and diminished prolonged ventricular overload damage. Moreover, it led to reduction of in-hospital stay promoting a more physiological social inclusion and a normal school education.

Growing up also means awareness of personal health conditions and of the consequences on everyday life. Several studies tried to assess how cardiopathy can influence life in congenital heart disease.[24-26] Quality of life and disease-related quality of life are wide concepts that are difficult to define exhaustively and deserve a multidisciplinary team composed not only by cardiologists but also by psychologists, neurophysiologists, social workers, obstetricians, gynecologists, experts in human science; moreover, their meaning is not univocal and immutable, but on the contrary it constantly changes during life, handling with expectations shaping differently during lifetime. *Temporal perspective* is particularly important in population with grown-up congenital heart (GUCH) because medical work-up of these patients does not end with surgical correction. Clinical problems, even those at long term, are nowadays better known.[27] Subsequently we improved preventive and therapeutic possibilities even in complex congenital cardiopathies as tetralogy of Fallot, transposition of great vessels, left ventricle outflow tract obstruction, univentricular heart disease and we can now define a post-surgical natural history of these patients recognizing risk factors for heart failure and sudden cardiac death. Raising up interest involves the improvement of clinical outcome and its reflection on the quality of life.[28-31]

## How these clinical successes produce a better quality of life

At first, we focused on objective and subjective parameters that can influence the quality of life: school education, work, family, medical care, but also self-perception and evaluation, disease-related symbols, cultural background and life-style of the control group.[32] In these patients medical and surgical history (determined by anatomy of disease, hemodynamic condition and surgical technique) intertwine with biological and social background.[33]

With regard to biological history, milestones as puberty, sexual development, pregnancy, risk of recurrence of disease in the offspring become important and produce peculiar psycho-physical adaptations.

Social history of these patients is markedly influenced by work-related issues and the need of medical care to preserve performance.[34] Psychological history is determined by structure of personality, psycho-affective relationships and the mental and emotional management of the cardiopathy within the family.[35]

Using various structured interviews, many data have been collected regarding external life conditions, interpersonal relationships and psychosocial status, but results are conflicting: some studies reported no significative differences between GUCH population and

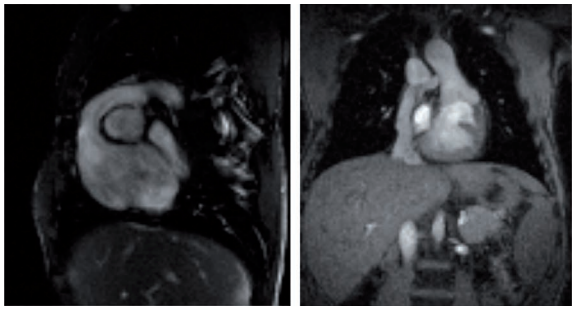


**Figure 1. Evolution of cardiac surgery; from atrio- to cavo-pulmonary anastomosis in Fontan operation.**

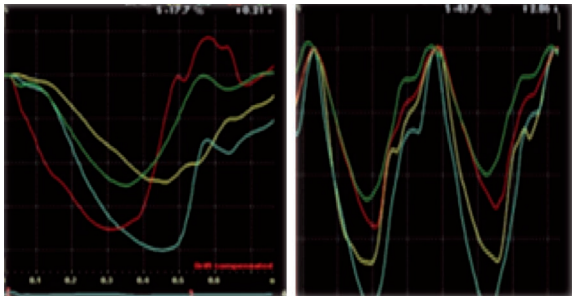


**Figure 2. Tissue Doppler strain imaging: right ventricular desynchrony. Differences of time to peak systolic strain right ventricular free wall and septal segments after surgery (on the left) compared with normal subject.**

healthy controls, maybe because patients may adapt over time to their physical status and denial is a common behavior to normalize functioning.[36] Other studies, on the other hand, highlight how congenital heart disease patients need more time in achieving schooling goals compared to healthy controls, along with lower graduation rate and inadequate job in relation to their educational level; difficulties in having stable relationship out of family network; discomfort to define and communicate a corporal image of themselves due to surgical scars. Different results can be explained by distinct models of the studies, different statistical sample regarding complexity of heart diseases and disparities in definition and measurement of quality of life.

Recently the APPROACH-IS Study (Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease - International Study) tried to overcome these limitations. This cross-sectional multilevel study enrolled with a standardized protocol more than 4000 patients belonging to 15 different countries and 5 continents, excluded Africa, to investigate the association between characteristics of the patients and quality of life, the international variation in quality of life and its relationship to country-specific features.[37] Firstly, all participants accepted the conceptualization that quality of life is *the degree of overall life satisfaction that is positively or negatively influenced by individuals' perception of certain aspects of life important to them, including matters both related and unrelated to health*. To detect quality of life 14 Centers utilized the *linear analog scale* and the *satisfaction with life scale*. The severity of cardiac anomaly was also considered and cardiopathies were clustered in simplex, moderate and complex. Level of general national happiness, included six cultural dimensions, was derived from the World Happiness Report. The study showed that patients generally have good quality of life and differences in perception are related to the patient more than to country.

Many of these studies, anyway, even if wide and accurate, are based on self-reported questionnaires, written out to detect objective functions, but scarcely tailored to focus on personal elements like the integration in the cultural and ethical environment, goals, expectations, standards and concerns of the patients. Only rarely they are supported by *face-to-face interviews* with experts that deepen the relationship of each patient with his/her own disease, and not only with the cardiopathy.[24]

## Cognitive abnormalities in population with grown-up congenital heart

The etiologic factors contributing to modify the integrity of brain in patients with congenital heart disease can be related to native congenital heart defect, because of persistent hemodynamic and hematologic effect of the disease, or to cardiac surgery.[38] At birth, cerebral abnormalities are more frequently seen in babies with hypoplastic left heart syndrome and coarctation of the aorta.[39] In patients with chromosomal abnormalities, particularly trisomy 21 and deletion on chromosome 22q11 (DiGeorge syndrome), the neurodevelopmental outcome seems to be related more to genetic factors than to the associated cardiac defect.

Congenital heart diseases characterized by hypoxemia and cyanosis with polycythemia and microcytosis are at risk of cerebral accident particularly during blue spells or increased blood viscosity conditions. Severe metabolic acidosis secondary to hypoxemia strengthens the negative effects of ischemia on glial and cerebral vascular cells. Early surgery (from neonatal period up to first trimester of life) prevents cerebral complications particularly in patients with transposition of the great arteries avoiding hypoxia and persistent metabolic acidosis and it forestalls blue spells in patients with tetralogy of Fallot.

No additional risk of cerebral injury is present in acyanotic congenital diseases in the absence of severe cardiac dysfunction.

Surgical correction of many congenital heart diseases requires cardiac arrest and measures to protect cerebral structures such as cardiopulmonary bypass and deep hypothermia. Both these measures are not free of cerebral side effects, because of the risk of microembolism during bypass, the uncertain optimal temperature to obtain a safe cardiac arrest period, and the activation of a variety of inflammatory pathways.

Although the vast majority of children with congenital heart disease have normal outcome, as group they generally show high rates of neurodevelopmental impairment, which include mild deficits in cognition, attention and neuromotor functions. Many studies report a positive correlation between the level of cognitive ability and the cardiac clinical severity.[40-46] Anyway complete evaluation of neurocognitive performance made by expert neuropsychologists is rare; often it is limited to IQ determination, that is mildly reduced in cyanotic patients. The IQ measure however is not sufficient to investigate the cognitive domain and a more exhaustive neuropsychological investigations can reveal an impairment of cognitive abilities such as executive functions and calculation. Executive functions are those involved in complex cognitions, such as solving novel problems, modifying behavior in the light of a new information, generating strategies or sequencing complex actions. Neuropsychological evidence suggests that executive processes are intimately connected with the intact function of the frontal and pre-frontal cortices. In apparently normal subjects who had a successful cardiac surgical correction, an exhaustive neuropsychological assessment

can reveal impairment of specific cognitive functions, which can be worsen by psycho-social conditions.[47]

Knowledge of the cognitive functions is important to implement adequate preventions and support measures with consequent improvement in the quality of life of these patients.

Maria Areias[25] found 19.7% lifetime prevalence of psychopathology in a cohort of 110 patients, more in females (27.6%) than males (13.9%), even if the perception of quality of life in congenital heart disease (CHD) patients was generally higher compared to that of the general population of her country (Portugal), but it was worse in complex forms. A review of Linda Pauliks[48] examined the evidence of higher incidence of depression in CHD patients compared with general population as a consequence of early exposure to stress in infancy due to separation from the parents during hospitalization, medical and surgical treatments, multiple hospitalizations, and reoperations. She found that higher risk to develop mental health problems was not related only to the economic and social circumstances. Experimental animal models showed that stress, induced early in life, produces anatomical modifications of hippocampus area of the brain, which is involved in the serotonin pathways. In humans, as in other mammalian species, serotonin plays a modulatory role in almost every physiological function. Furthermore, serotonergic dysfunction is thought to be implicated in several psychiatric and neurodegenerative disorders.

## Sexual functioning, fertility and pregnancy

Sexual health is an important component of quality of life for both normal people and patients with heart diseases. In adolescents and young adults with congenital heart pathologies, physical and psychological factors may contribute to an impairment of full expression of sexuality and to sexual dysfunction. Among GUCH men and women, sexuality problems are more frequent than in healthy people[49] and involve erectile dysfunction, intercourse satisfaction in man and desire, arousal and pain in female with inadequate overall satisfaction in both, even in asymptomatic or mildly symptomatic subjects without heart failure or life-threatening arrhythmias.

The patients however, rarely speak about this topic during follow-up visits, except in the most severe dysfunctions. Reported deaths or strokes during sexual activity among adult with CHD (ACHD) are rare,[50] but 9% of women within this population reported symptoms during sexual activity, included dyspnea, perceived arrhythmia, increased fatigue or syncope. Symptoms were more common in patients with severe lesions, worse functional status or cyanosis; among men with ACHD, 9% reported dyspnea or subjective arrhythmias and 5% reported chest pain during sexual activity. Again, symptoms were more common in patients with greater functional impairment (New York Heart Association class III).[51] Sexual activity is safe in most adult patients with CHD, except those with significant pulmonary hypertension, cyanotic heart disease, severe left-sided heart outflow obstruction, uncontrolled arrhythmias and anomalous coronary artery with interarterial course, in which the safety of sexual activity is less certain or unclear.[52]

Rheumatic cardiopathy almost disappeared from mid-'70s in western countries, so congenital heart disease is actually the most frequent cardiovascular disease present during pregnancy, after hypertensive disorders.

Unpaired fertility is uncommon among women with congenital heart disease (5%); nonetheless menstrual cycle disturbances are more frequent and they can provoke conception difficulties that require gynecological intervention.

The complexity of cardiac disease, its consequences and the post-surgical aftermaths determine the possibility of conceiving and, above all, of carrying pregnancy to term: in the review of ZAHARA Investigators Group, Drenthen and Colleagues found 15% of miscarriages and 5% of abortions.[53] Euroscan Group determined the effect of prenatal diagnosis of fetal cardiac anomaly on outcome of the pregnancy: they collected 709,030 prenatal screening in 2 years of observation and found 613 (3.5%) cardiac defects. 48% of women with a positive screening for cardiac anomalies interrupted the pregnancy.[54]

Maternal oxygen saturation is the major determinant of the outcome of the pregnancy: in women with an aortic oxygen saturation below 75% in fact, only 20% of pregnancies end in delivery of a living baby.[55]

Gestation in women with congenital heart diseases has moreover higher risk of preterm delivery and intrauterine growth retardation (IUGR); it also presents an increased teratogenic risk due to maternal medications and an enhanced recurrence rate of cardiac defect in the offspring.[56,57]

In cases where prematurity is associated with IUGR, the risks of complications and severe consequences for the newborn, eventually death, are significantly high. The predictors of maternal complications, like the New York Heart Association (NYHA) functional Class greater than II, cyanosis or relevant left ventricle outflow tract obstruction, are the same for the fetal outcome.[58] Moreover, a reduced gestational growth can affect long-term neurological, vascular, endocrine and metabolic development, causing diabetes or dyslipidemia. Recurrence of in-born heart anomalies is greater in the offspring of mothers with congenital heart disease. Prevalence of cardiac defects shows high variability but strong familial clustering in first-degree relatives, ranging from 3-fold to 80-fold

compared with the general population.[59] For this reason, it is important to perform fetal echocardiography in women with congenital heart disease. The accuracy of the exam is elevated after the 16th gestational week (g.w.), even if a normal nuchal translucency between 12th and 13th g.w. has a very high negative predictive value in detecting fetal cardiac defects and can be useful in anomalies with greater risk of recurrence. The CARPREG Investigators Study[60] analyzed prospectively 599 pregnancies in 562 women with heart disease. 74% of the patients had congenital anomalies (patient with Eisenmenger syndrome were excluded from the study). At the multivariate analysis, predictive risk factors for major event (*i.e.* heart failure, arrhythmias, stroke and maternal death) resulted in a previous cardiac major event, the severity of the obstruction of the left ventricle outflow tract, the dysfunction of the systemic ventricle, a reduced NYHA functional Class and the presence of cyanosis.

More recently the CARPREG II Investigators examined the temporal trends in complications:[61] predictors of cardiac complications were identified and incorporated into a new risk index. 16% of pregnancies in women with congenital heart diseases were complicated by cardiac events, mainly arrhythmias and heart failure: the overall rates of cardiac complications during pregnancy did not change over the years. Ten predictors of maternal cardiac complications were identified: prior cardiac events or arrhythmias, poor functional class or cyanosis, high-risk valve disease/left ventricular outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions, mechanical valves, high-risk aortopathies, pulmonary hypertension, coronary artery disease and late pregnancy assessment.

Maternal cardiopathies can also be classified on the basis of their specific risk: during pregnancy bicuspid aortic valve, moderate stenotic aortic valve, pulmonary valve stenosis, small or repaired atrial and ventricular septal defects, tetralogy of Fallot after optimal correction, mitral valve prolapse and small or closed ductus arteriosus are at low risk (probability of maternal cardiac complications less than 1%); Eisenmenger syndrome, valvular atresia, double-outlet right ventricle, d-transposition of great arteries with associated anomalies, defects corrected by Fontan's, Rastelli's and atrial switch operations, Marfan syndrome are at high risk (risk of maternal cardiac complications >2%).

After atrial switch operation for transposition of great arteries, the risk of complications during pregnancy appears elevated. Using a multicentric, nationwide registry (CONCOR), ZAHARA Investigators[62] collected 70 patients with Senning (23%) or Mustard repair for TGA: 28 patients had 69 pregnancies with 17 spontaneous miscarriages and three elective abortions, frequent arrhythmias (above all supraventricular tachyarrhythmias) and 10% of pre-eclampsia. Obstetrical complications like premature rupture of membranes, preterm labor and delivery were also frequent.

In patients with dysfunction of the systemic ventricle, the volume overload during pregnancy may precipitate a labile condition. A systematic review of the literature about pregnancy in women with Fontan circulation was written by Garcia Ropero:[63] 255 pregnancies in 133 women with Fontan were collected; they produced 115 live births (45%), 115 miscarriages (45%), 19 elective terminations (7%), 2 stillbirths, and 1 ectopic pregnancy. Atrial arrhythmias (3-37%) and heart failure (3-11%) were the most common cardiac adverse events, but no maternal death was reported. 14% of women had post-partum hemorrhage; 59% of the live births was premature (59%) or small for gestational age (20%); neonatal mortality was 5%. Long-term maternal sequela has still to be verified.

Eisenmenger syndrome is defined by increased pulmonary vascular resistance and pulmonary pressure up to systemic values. This, in the presence of intra- or extracardiac communications between arterial and venous system, causes reversal of blood flow and cyanosis.

The presence of Eisenmenger syndrome represents a contraindication to pregnancy because it entails high risk of morbidity and mortality ranging between 30 and 50%. Our experience, above all during last decade, showed that prognosis in these patients can improve with a careful follow-up during pregnancy, a mindful planning of time and mode of delivery, and an attentive monitoring of hemodynamic conditions in Intensive Care Unit during the first week after delivery, when the risk of pulmonary hypertensive crisis is elevated due to sudden changes in hormone balance typical of puerperium.

The reduction of peripheral resistance during pregnancy is not counterbalanced by the reduction of pulmonary vascular resistance which are both, by definition, fixed in Eisenmenger's syndrome. This leads to the increase of right to left shunt and worsens oxygen saturation, finally causing increment of erythrocytosis and thus of thrombotic risk (already physiologically increased during pregnancy), and reducing fetal oxygenation. Prophylactic anticoagulant therapy must be used with caution: low-molecular weight heparin may prevent thromboembolic complications, but subsequent bleeding, particularly after delivery, has been reported with significant blood loss and transient blood pressure drop.

Moreover, recent studies supported the use of selective pulmonary vasodilators in pregnancy and confirmed the good tolerability of the analogous of the prostacyclin (*i.e.* iloprost, epoprostenol), while few data are available on the endothelin-receptor antagonists (as bosentan) during gestation.[64-74]

Pacini[57] *et al*. retrospectively examined the clinical

history of 415 women affected by Marfan syndrome. Women over 18 years of age were divided into two groups: 85 underwent pregnancy (160 pregnancies and 135 live births), 68 did not. Major aortic adverse events (aneurysmatic dilatation, rupture) comparison between the two groups showed 7 events during 160 pregnancies (4.4%) and 17 events during the 1870 years of follow up (0.9% per year of follow up) in the pregnancy group. In the group without pregnancy, 14 aortic complications occurred over 940 years of follow-up, with a risk of adverse events of 1.5% per year of follow-up. Pregnancy was associated with a 5-fold increased risk of aortic complication, which did not translate into increased risk during life, but led to a different survival curve in the two groups. Additional, but not less important, risks in patients with congenital heart diseases are represented by infective endocarditis, paradoxical embolism and possible adverse effects of medication on the fetus.

Vaginal delivery is generally recommended, except for aortic dissection, Marfan syndrome o bicuspid aortic valve with significant dilatation of the ascendant aorta, acute intractable heart failure, severe forms of pulmonary hypertension (including Eisenmenger's syndrome) and pre-term labor in patients on oral anticoagulation therapy.

Induction of pre-term delivery is rarely necessary, but it can be taken into consideration in the presence of signs of heart failure. Delivery can be performed on the left side to minimize hemodynamic consequences of uterine contraction in supine position. Use of forceps shortens the expulsion stage of delivery thus reducing maternal efforts.

Puerperium is the period at higher risk of complications: cardiac output suddenly reduces by 37%, cardiac contractility decreases as well (even if it is reversible), estrogens drop and adrenergic hormones raise: patients at higher risk are those who, during pregnancy, presented arrhythmias, pulmonary hypertension or moderate or severe ventricular dysfunction. Deaths among patients with Eisenmenger syndrome occur typically during the first two weeks after delivery because of the boost of fibrinoid necrosis involving pre-acinar arterioles as a consequence of the hormonal storm in puerperium.

Population of pregnant women with congenital heart diseases is growing and related problems are more frequent and complex to solve. Multidisciplinary management and support of pregnancy is desirable, and it should ideally start before conception and continue even after the delivery to enhance safety for both mother and child.[71]

## Contraception

With regard to contraceptive methods, GUCH women can be divided into groups with different risk of adverse events according to the type of cardiopathy and clinical condition: operated women without cyanosis or pulmonary hypertension have low risk of severe adverse event as heart failure, sustained arrhythmias, thromboembolism and death but they have nonetheless a higher risk of infective endocarditis; women with post-surgical sequelae, cyanosis, pulmonary hypertension and ventricular dysfunction have an increased risk of adverse events related to the use of combined (estroprogestinic) oral contraceptives, lowered with the progestin-only pills. Intra-uterine devices increase risk of infective endocarditis.

Importantly, half of women CHD have limited knowledge of contraceptive methods and of risks connected to pregnancy due to insufficient sensitization made by doctors.

In the report on *Contraception in Women With Congenital Heart Disease*,[75] that examined two important third level GUCH Center, 20% of the patients used a contraceptive method that was contraindicated according to their specific cardiopathy and 28% of the patients with a cardiopathy at high risk during pregnancy did not use any contraception method but had sexual activity.

Oral contraceptives (combined or progestin-only), condoms, intrauterine devices were the most used contraceptive methods.[76]

## Gender differences

During the last years, gender differences in cardiopathies were explored focusing on physiopathology, clinical presentation, management and prognosis of ischemic heart disease. In GUCH community, few data were collected and moreover, they are limited and derived from epidemiologic studies: the major prevalence of simple congenital heart diseases (*i.e.* atrial septal defect, patent ductus arteriosus) and inflow anomalies in women and of complex cardiopathies like univentricular heart and outflow tract alterations in men is well known. It is still not clear whether differences in myocardial structure and hormonal factors play a role in determining long-term clinical history in women with congenital heart disease, influencing the adaptation to volume and/or pressure overload, the development of pulmonary hypertension and arrhythmias occurrence, that represent the most significant disease factors in long-term follow-up.

Myocardial mass correlates with body surface area, so mean values result lower in women than in men. Furthermore, female myocytes have more contractility compared to male fibers of the same age; this difference lasts over time and it can be explained by differences in glycolytic activity and mitochondrial metabolism in cardiomyocytes.

Adaptive response of ventricular myocardium to volume and/or pressure overload is also different. In female athletes, left ventricle volume raise is proportionally lower than in male athletes adjusted for the same type of physical activity. Additionally, it has been shown a different pattern of hypertrophy in women, in which concentric hypertrophy is prevalent along with lower cavity dimension and longer preserved systolic function.

Among patients who underwent an aortic valve replacement at Mayo Clinic, female sex was an independent predictor of ejection fraction (EF) improvement after surgery in patients with preoperative EF <45%.[77] The post-surgical history in women with tetralogy of Fallot was characterized by a more favorable morpho-functional condition of the two ventricles, with less impairment of the left ventricle, compared to men[78] (Figure 3).

Pregnancy, particularly multiparity, can be a key element in clinical history in GUCH women. In patients with tetralogy of Fallot, women with one previous pregnancy showed no significant differences in echocardiographic morpho-functional features compared to nulliparous women and to men. Patients with 2 or more previous pregnancies most frequently complained of fatigue and palpitations, and echocardiography showed frequently mild and moderate degrees of tricuspid regurgitation with enlargement of the right atrium, dilatation of the right ventricle, limited pump ability and increased pulmonary arterial pressure.[79]

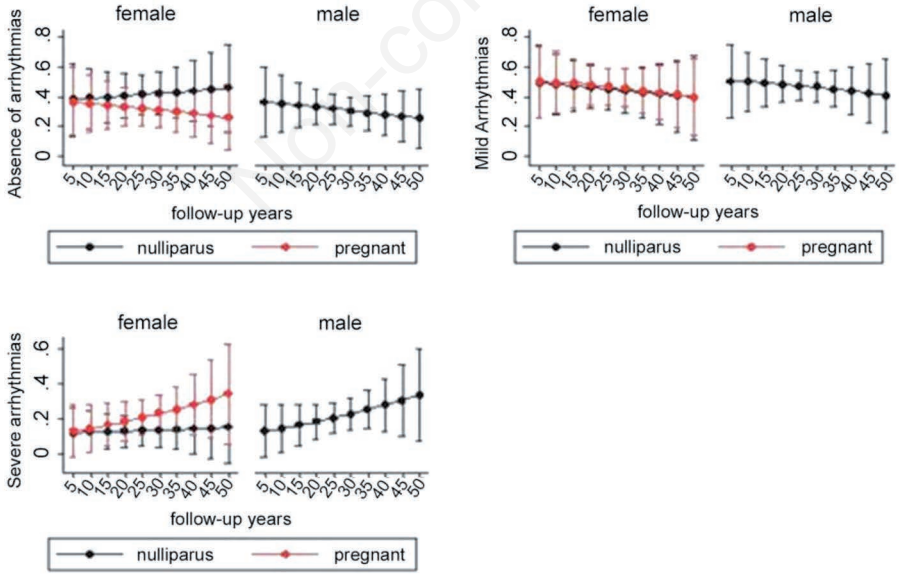
It is difficult to say which part of these differences can be explained by genetics and how much it depends on sexual hormone action.

Estrogen receptors regulate also the expression of genes implicated in risk factors for cardiovascular diseases: hypertension, diabetes, metabolism and lipoproteins expression. Estrogen receptor α entails 3 different direct effects on vessel wall: i) acceleration of re-endothelization; ii) modulation of NO production in endothelial cells; iii) inhibition response to vascular insult.

In women it has been shown a strong association between arterial hypertension and early death and an even stronger relationship (much stronger than in men) with cardiovascular diseases.

In Framingham study, hypertension represents the most important independent risk factor in women (more than in men), together with age. After the menopause, blood pressure raises and overcome men values. Similarly, sympathetic activity increases. Total cholesterol/high-density lipoprotein cholesterol ratio together with blood level of lipoprotein(a) is the strongest risk factor for coronary heart disease after age: differences in expression of lipoproteins are gender-dependent. Lipoprotein(a) is involved in atherogenic and thrombogenic activity; its concentration is hereditary and, differently from other plasma lipids whose concentration changes during life, it remains stable from early childhood. The presence of diabetes enhances the risk of fatal coronary disease more in women (3-7 folds) than in men (2-3 folds). This illness boosts the action






Severity of aritmia according to follow-up time, with 95% C.L.

*Daliento L, Dal Bianco L, Bagato F, Secco, Sarubbi B, PLoS One 2012;7:e49729.*

**Figure 3. Gender differences and role of pregnancy in the history of post-surgical women affected by tetralogy of Fallot.**

of other risk factors and, interfering in the hormone-receptor bind, it alters the protective action of estrogens thus promoting the formation of atherosclerotic plaque; diabetes also increases fibrinogen levels and reduces fibrinolysis enhancing thrombotic risk. Atherosclerotic disease can involve also female GUCH population and regular counselling is needed to promote healthy life style, to preserve surgical results and to prevent degenerative vascular processes.

Recently Oliver[80] conducted an observational single-center study of 3311 consecutive adult patients with congenital heart disease with a follow-up of 25 years. He found that long-term relative survival was significantly worse in women than in men; moreover, severe pulmonary hypertension was more frequent in women while alteration of aortic wall and endocarditis were more common in men.

Mortality due to heart failure is lower in women than in men in non-ischemic heart diseases, but it becomes higher in ischemic cardiopathy.[81]

Frequently GUCH women (as occurs in women with ischemic heart disease) do not benefit from tailored follow-up, focused on gender specificity and on age-related specific features that are more complex in women than in men. In this population, the importance of prevention of atherosclerotic disease that represents an additional risk factor in their natural or post-surgical history, must be discussed.

It is thus necessary that training of GUCH cardiologists takes into consideration the raising presence of atherosclerotic disease that impacts on clinical outcome and prognosis of patients with congenital heart disease. New pilot studies and clinical trials are nonetheless necessary to clear how specific hormones can influence gene expression and modify cellular function and metabolic, electrical and hemodynamic risk factors.[82] Gender represents a prognostic factor and it is necessary a tailored clinical follow-up that considers not only traditional risk factors related to congenital cardiopathy and to its surgical correction, but also prevents and treats cardiovascular degenerative illness, involving coronary, peripheral and pulmonary vessels.

Gender differences are even wider in social and economic environment: women have more difficulties in finding an employment compared to men of same educational level and they hardly obtain a job position adequate to their educational level. This is more evident in nations with underprivileged welfare, but also in prosperous countries during periods of economic crisis, as highlighted in the study by Sluman *et al.*:[83] the study was conducted on a huge number of patients belonging to a wealthy country for work perspectives and social assistance: 16% of men affected by congenital heart diseases were unemployed compared to 7% of men of the control group, and to 35% of female GUCH patients that more frequently had a part-time job. Having children did not seem to be a discriminant factor in finding an employment for GUCH women compared to general female population.

The chance to find an employment decreases as the complexity of cardiopathy raises; anyway, women have lower probability to find a full time, gratifying and well-salaried job independently from their clinical conditions.[84] Moreover among GUCH women there is the highest percentage of single and divorced and a lower esteem of the body because of scars or of skeletal modifications of the thorax.

The development of programs of follow-up, which involve other specialists such as gynecologists and psychologists, and the strengthening of social services significantly reduce gender differences in terms of quality of life, and promote the same odds of survival as well as a better control of complications and sequela.

## New models of information

*...they, the Babylonians, would take their sick to the market place, because they didn't have doctors; then people would go to visit who was sick and if they had the disease before or knew someone who suffered a similar condition they would give him advice about his disease. This would bring the people closer to the sick and they could recommend or give advice to those who suffered as they had and in turn could learn about other diseases that other people were suffering from. (Herodotus, Histories, 1,6,197).*

Patients have always needed to share their experience; nowadays this happens in an easier way thanks to new methods of communication as on-line forums and voluntary associations.

During the last years several initiatives both public and private raised, promoted above all by the families of GUCH's patients. The opening of socio-cultural associations and the fundraising for research and for improvement of the structures tried to offset the neglect of the institutions and strongly helped to spread the knowledge of specific problems, enhancing awareness in health authorities.

## How to improve assistance

Quality of care can be measured in terms of structures (healthcare and non-healthcare professionals, presence of dedicated services), processes (time and mode of follow-up, type of intervention) and results (mortality and morbidity rate, quality of life).

Development of guidelines about training and specialization level of hospitals and territorial services could improve quality of assistance in all the three fields.

The guidelines should firstly recognize the subspecialty and define the objectives to achieve during the training, considering that different backgrounds (pediatric *versus* cardiological one) lead to different careers. Secondly, they should uniform the management of follow-up to prevent clinical deterioration and sudden death: during transitional age from childhood to adolescence, in facts, there is a drop-out of the patients in follow-up and the raise of emergency hospitalization. Thirdly, guidelines should define homogeneous evaluation scales by involving different professional profiles and different institutions.

In the last two decades the most important scientific societies (Canadian Society of Cardiology, European Society of Cardiology, American College of Cardiology) wrote different Guidelines that contribute to spread the knowledge of GUCH population and made cardiologists aware of the need of adequate assistance.[85-87]

Guidelines importantly do not have any legal value, but they are taken into consideration in the court.

Moreover, they are not simple descriptions and classifications of congenital heart diseases, but they try to give practical advice to uniform the management, following an international-shared knowledge.

Guidelines also design a multidisciplinary interventional model to improve quality of life of GUCH community, in different fields: sport and work eligibility, assistance issues, sexuality and procreation; they highlight the necessity of following people with congenital heart disease during the growth from childhood to adult life; they contribute to professional training of experts and spread new diagnostic and therapeutic procedures. Anyway, few years ago a survey of the European Society of Cardiology documented poor adherence to Guidelines from European cardiologists.[88]

Lacking clinical trials of numerous cohorts, international registries and multicentric prospective studies on the efficacy of treatment, recommendations of level of evidence A are currently absent, and level B are very few in European guidelines (more present in American ones). Most indications are based on consensus of experts coming from different institutional, social and cultural backgrounds (America or Europe) that produce different contents: American guidelines for example have a comprehensive introduction, the European ones are more focused on *resolving clinical questions* and on new non-invasive diagnostic techniques, promoting functional quantitative analysis; they are also less restrictive in the prophylaxis of infective endocarditis; furthermore American and European guidelines have different positions in sport eligibility: European guidelines are more conservative in intense physical activity, probably because they are influenced by the Italian experience.

GUCH people should be periodically reassessed by specialists trained in ACHD in designated centers but, still today, a relevant number of patients is lost during follow-up with significant clinical and socio-economic consequences.

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