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Discovering Thoughts, Inventing Future

VOLUME 14

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GYNECOLOGY AND OBSTETRICS

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# Incidental Finding of Panhypogammaglobulinaemia in Pregnancy-an Extremely Rare Condition

By Crishan V. Haran & Dr. Sabaratnam Ganeshanathan

*Summary-* A 22 year old lady, G2P0 presented at a 311 weeks of gestation with an abnormal group and antibody test found incidentally during routine 28 week blood testing. She reported no past medical history apart from medication controlled gestational diabetes and denied any family history of autoimmune diseases. She was subsequently diagnosed with panhypogam-maglobulinemia. After consultation with an immune-ologist, a number of blood investigations were undertaken, all of which were negative, except for an MRI which showed a possible small thymoma. All fetal ultrasounds were unremarkable. Given the importance of transplacental immunoglobulin (Ig) transfer in the third trimester and the concern of serious infection during pregnancy she has was commenced on intravenous immunoglobulin (IVIg). After a loading dose of IVIg (0.6mg/kg) and a subsequent dose (0.4mg/kg) her Ig level was 10. She was administered a third dose and it was decided that her Ig levels be monitored weekly and IVIg only administered should her levels drop below 7. Since her Ig levels dropped to 6.9g/L at 37 5 weeks of gestation, she received another dose (0.4mg/kg). She underwent a normal delivery at 391 weeks and was diagnosed with a thymoma postnatally.

*GJMR-E Classification : NLMC Code: WP 660*



INCIDENTAL FINDING OF PANHYPOGAMMAGLOBULINAEMIA IN PREGNANCY - AN EXTREMELY RARE CONDITION

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# Incidental Finding of Panhypogammaglobulinaemia in Pregnancy-an Extremely Rare Condition

Crishan V. Haran <sup>α</sup> & Dr. Sabaratnam Ganeshanathan<sup>ο</sup>

**Summary-** A 22 year old lady, G2P0 presented at a 311 weeks of gestation with an abnormal group and antibody test found incidentally during routine 28 week blood testing. She reported no past medical history apart from medication controlled gestational diabetes and denied any family history of autoimmune diseases. She was subsequently diagnosed with panhypogam-maglobulinemia. After consultation with an immune-ologist, a number of blood investigations were undertaken, all of which were negative, except for an MRI which showed a possible small thymoma. All fetal ultrasounds were unremarkable. Given the importance of transplacental immunoglobulin (Ig) transfer in the third trimester and the concern of serious infection during pregnancy she has commenced on intravenous immunoglobulin (IVIg). After a loading dose of IVIg (0.6mg/kg) and a subsequent dose (0.4mg/kg) her Ig level was 10. She was administered a third dose and it was decided that her Ig levels be monitored weekly and IVIg only administered should her levels drop below 7. Since her Ig levels dropped to 6.9g/L at 37 5 weeks of gestation, she received another dose (0.4mg/kg). She underwent a normal delivery at 391 weeks and was diagnosed with a thymoma postnatally.

## I. BACKGROUND

This case is particularly interesting not only because it is very rare but presents an interesting clinical challenge. Although panhypogammaglobulinemia is a well described condition, only a few published cases of it occurring in pregnancy exist. Additionally, among the few cases published there is a disagreement as to whether treatment is required.

## II. CASE PRESENTATION

The patient is a 22 year old woman of subcontinental Indian origin who at the time of diagnosis was 30 weeks pregnant with her second pregnancy. She has no past history of any significant infections, neither recently nor in her childhood and denied any past operations or hospital admissions. After a routine 28 week oral glucose tolerance test during her second pregnancy she was diagnosed with gestational diabetes. After a trial of diet control, she was started on metformin at 34 weeks maintained adequate control of her blood sugar levels. Apart from her recent gestational diabetes and a first trimester miscarriage in the first

trimester of her first pregnancy, she has no significant past medical history of note. There is no significant family history of note and prior to pregnancy she denies any abnormal weight loss, fevers, fatigue and night sweats. There is no history of consanguinity and she is a non-drinker and non-smoker. She has no known drug allergies and apart from metformin she also took a pregnancy multi-vitamin,

Her pregnancy was the result of spontaneous conception and all antenatal ultrasounds were unremarkable. At 223 weeks a morphology revealed no abnormalities and a cephalic lie with a posterior placenta. Her 45 week routine blood tests revealed she was rubella non-immune and had low globulins (16g/L (20–36)). Urinalysis performed showed no abnormalities.

## III. INVESTIGATIONS

At 311 weeks her blood tests showed undetectable levels of Igs (IgG <1 g/L(7 -16); IgA <0.06 g/L(1 - 4); IgM 0.07 g/L(0.4 - 2.3) ).

MRI (323 weeks) showed a mass within the anterior mediastinum in the expected location of the thymus measuring 37mm in width by 18mm in maximal AP dimension. The appearance is somewhat non-specific, with a differential line between a thymic remnant and a thymoma. There are no overly aggressive features to suggest a thymic carcinoma.

Ultrasound (322 weeks) did not show any placental oedema or other obvious placental pathology demonstrated.

A postnatal CT confirmed the presence a thymic mass which intraoperative histology demonstrated to be a thymoma.

Other investigations (FBC/ELFTs, Urine Protein, Serum EPP/Urine EPP, ANA/ENA C3/C4, Lymphocyte subsets, CRP/ESR, HIV, Faecal a1anti-trypsin, urinalysis for EPP and the presence of Bence-Jones proteins) performed to exclude SLE, Leukaemia, Lymphoma, Multiple Myeloma and nephritic syndrome are all negative.

## IV. DIFFERENTIAL DIAGNOSIS

- Good Syndrome (thymoma with immunodeficiency)
- CVID
- Primary or secondary nephrotic syndrome.

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## V. TREATMENT IF RELEVANT

After discussing the treatment options with the immunologist it was decided that the patient would undergo intravenous administration of Ig. Given her extremely low levels of Ig, a loading dose of 0.6mg/kg was administered at 331 weeks. Apart from the patient suffering from tachycardia and shivering, the infusion continued uneventfully. Three more infusions were administered at a lower dose of 0.4mg/kg at 343, 351 and 385 weeks with no adverse effects noted. The fourth dose was administered at approximately 39 weeks since her Ig level fell below 7. Peripartum antibiotics were prescribed for seven days and the newborn's Ig levels were checked postnatally. These were all normal. As per instruction of an immunologist the patient was administered a tetanus vaccine postnatally and tetanus antibody levels were measured four weeks later to see if an immune response was mounted. Surgical removal of the thymoma discovered on MRI and CT was undertaken with no complications.

## VI. OUTCOME AND FOLLOW-UP

Four days after the admission the loading dose of IVIg the patient's blood tests revealed a significant improvement in plasma Ig levels (IgG 8.0, IgA <0.06, IgM <0.05). After the second dose her bloods showed further improvement (IgG 10.0, IgA <0.06, IgM <0.05). However, her Ig levels dropped to 6.9g/L at 37 5 weeks of gestation hence she received another dose (0.4mg/kg).

After delivery the infant's Ig levels were monitored and found to be progressing as expected of a normal child. The patient was followed up by an immunologist and a CT scan confirmed to diagnosis of a thymoma. This was removed surgically and histologically confirmed as a thymoma. The patient has recovered well from the procedure and has had no long term side effects.

## VII. DISCUSSION

Good syndrome is an exceptionally rare condition characterised by a combination of B and T cell immunodeficiency and the presence of a thymoma. As a result of their immunodeficiency patients are susceptible to bacterial infection with encapsulated organisms as well as opportunistic viral and fungal infections (1). The presence of such a condition during pregnancy presents a unique challenge for treating conditions. Additionally there are very few published cases regarding thymoma related immunodeficiency in pregnancy with only one other case noted in the literature (2).

After confirming the presence of hypogammaglobulinaemia in our patient, a number of common causes such as HIV, myeloma and nephrotic syndrome were ruled out before a literature search for rarer causes

was undertaken. Although there are very few cases of hypogammaglobulinaemia reported on, some potentially treatable causes were identified. A 1977 case report describes three conditions related to placental oedema which may be responsible for Ig deficiency (3). These conditions, fetal transfusion syndrome, hydrops fetalis and congenital hepatic disease, and indeed placental oedema were ruled out by a normal ultrasound performed at 322 weeks. (2). To rule out the presence of a thymoma, an MRI scan was performed which demonstrated a small mass unable to be defined as either a thymoma or a thymic remnant. The presence of a thymic carcinoma was however ruled out.

Although cases exist where a hypogammaglobulinaemic mother was untreated during pregnancy and delivered a healthy neonate, a number of cases have demonstrated treatment with IV Ig is desirable as individuals are prone to serious infections and fetal loss (4-9). As demonstrated in a case published by Laursen and Chistensen (1973) neonates born to hypogammaglobulinaemia mothers are typically deficient in Ig (5). Given that it can take infants up to four months to produce adequate levels their own Ig, it is often necessary to provide IV Ig therapy to newborns as well(10). Despite being deficient in Ig at birth it seems likely from previous cases that the newborn will go on to produce normal levels of Ig once its own immune system become functional during the first six months of life (5).

Postnatally, mothers require further investigation of the cause of hypogammaglobulinaemia and may require ongoing IV Ig therapy. In our case a thymoma was discovered and surgical removal was undertaken. As expected from prior cases the delivery of the fetus was uncomplicated we do not believe her condition will have any lasting effect on the infant's health.

## VIII. LEARNING POINTS/TAKE HOME MESSAGES

- Any abnormalities found in routine blood tests during pregnancy need to be investigated and treated seriously
- There is a need for more cases of a similar nature to be published so that the best treatment can be determined.
- Currently, IVIg therapy is the mainstay in order to optimise fetal/neonatal outcome.

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## Medical Errors in the Private Sector where to?

By Tarik Y. Zamzami, Mohamed B. Gandeh & Haneen M. Shaheen

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**Abstract-** To study the issues of medical errors in the private health sector and determine the conviction rate in the decisions by specialty on the defendants from health professions. The total number of decisions issued by the Health Authority within five years 331 resolution and the conviction rate (Number = 192, 58%) were distributed into the following health facilities: private hospitals (n = 248, 74.9%), private clinics (n = 56, 16.9%) and private dispensaries (n = 27, 8.2%). Total 252 out of 845 of defendants health professions were convicted, they are distributed as follows: Doctors (n = 236, 93.7%), nurses and midwives (n = 13, 5.2%), technicians (n = 2, 0.8%) and other professionals (n = 1, 0.4%). The conviction rate in five years is on the rise and thus this is reflected on the trend of medical errors into upward in the private health sector.

**Keywords:** *condemnation, plaintiff right, decisions, judgments, health staff, mistakes, health facilities.*

**GJMR-E Classification :** *NLMC Code: WX 140, W 50*



MEDICAL ERRORS IN THE PRIVATE SECTOR WHERE TO?

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**Keywords:** *condemnation, plaintiff right, decisions, judgments, health staff, mistakes, health facilities.*

## I. INTRODUCTION

The role of private health sector is to provide the health care and services to a large segment of community through different health facilities. The total number of health facilities in the present from operating existing hospitals and dispensaries, and medical clinics is 487 health facility, and 81 health facility licensed under construction in the city of Jeddah, Saudi Arabia <sup>[1]</sup>. The medical work always aimed at the patient's best interests to make medical care for the diagnosis and treatment, but medical errors have become almost daily phenomenon and no longer confined within the health professions but become the public talk and newspapers. From here is evident to draw attention to the ends of the equation in the field of medical care provided by the private health sector and protect the patient from medical errors from the other side <sup>[2]</sup>. Medical Errors in content is affect patient safety and the doctor is in charge when breach his obligations literary and profession, and is not required to be wrong index whether simple or big, it's enough to be wrong and clear and direct result of the damage or the injury brought about by a doctor due to negligence and lack of follow-up or wrong behavior is not familiar for medical practice or work not in the field of specialization or without a license <sup>[2-4]</sup>. The Health legitimate authority board their role is in knowing the reasons and linked to get the truth as claim when you get damage or injury to the patient and that attributed the harm causes and distinguish them between the complication and the product of mistake and the adoption of why the product

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of mistake alone is a reason to harm standard in proving the causation between medical error and damage and the accountability is for their medical mistakes committed against patient in terms of physically, financially and morally <sup>[5]</sup>. So the objectives of this study: 1) To determine the percentage of the conviction in the decisions on the defendants doctors by specialty; 2) and to determine the percentage of disability and deaths and compensation in cases of medical errors in the private health sector.

## II. METHODOLOGY

This is a retrospective study issued by the Health Authority basic legitimacy on the medical errors cases and decisions in the private health sector Jeddah Saudi Arabia from 2007-2011. The study was approved by the Biomedical Ethics Research Committee Human Investigation at King Abdulaziz University (**Ref. No. 1084-13**). To determine the distribution decisions on health facilities and categorized by specialty. The verdicts results were studied on defendants health professions on "doctors, nurses, midwives and technicians" to know the number and percentage of convicts and compared to non-convicts. Also, the conviction of deaths and disability were studied from the decisions to know the amount of compensation as a result of medical errors. This study is based on statistical data analysis to know the conviction rate from medical errors and result from verdicts (condemnation in two rights together, plaintiff and public rights, or waiver plaintiff, and with no condemn or irrelevant in the two rights) on the defendants from health professions. Statistical analysis was performed using the package SPSS version 19 (SPSS, Chicago, IL USA). Data were presented as numbers (n), percentage (%), cumulative percentage and the trend. Chi-square test or Fisher's exact test for categorical data. The value less than (< 0.05) considered statistically significant.

## III. RESULTS

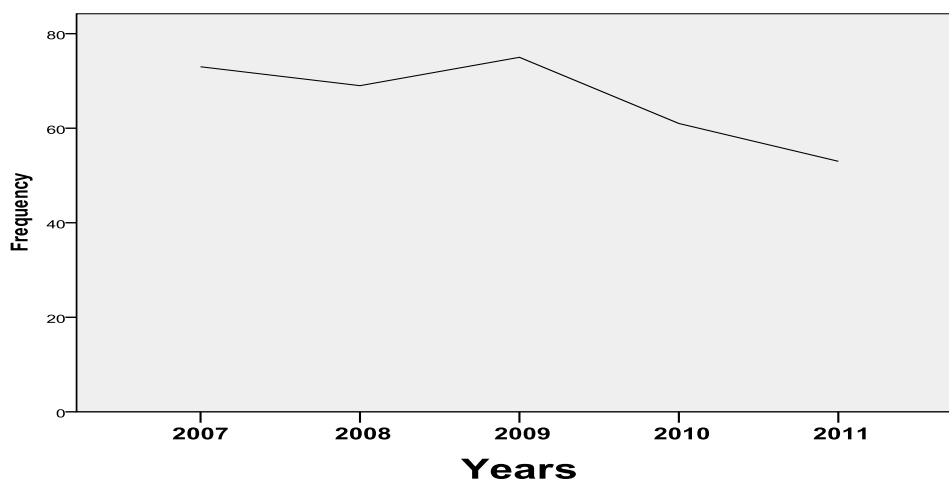
The total number of decisions issued by the Health Authority basic legitimacy within five years 331 resolution and the total of convictions (n = 192, 58%). **Table [1]** shows the number and percentage of convictions in the decisions, judgments or "verdicts" and compensations as a result of medical errors from each year from 2007-2011. The direction of decisions issued through five years where there was a higher proportion of decisions issued in 2009. The highest proportions of decisions were issued against private hospitals

compared to other health facilities as the following: clinics (n = 56, 16.9%) and private dispensary (n = 27, private hospitals (n = 248, 74.9%), private medical 8.2%) as shown in **Chart & Figure. [1]**.

*Table 1 :* Show the total number of decisions issued, verdicts & compensations within five

Years	2007 N(%)	2008 N(%)	2009 N(%)	2010 N(%)	2011 N(%)	Total N(%)
Decisions	73(22.1%)	69(20.8%)	75(22.7%)	61(18.4%)	53(16%)	331
Convictions	40(54.8%)	35(50.7%)	46(61.3%)	38(62.3%)	33(62.3%)	192(58%)
*Condemnation (two rights)	22(30.1%)	14(20.3%)	13(17.3%)	21(34.4%)	20(37.7%)	90(27.2%)
Conviction (Plaintiff right)	2(2.7%)	2(2.9%)	6(8%)	2(3.3%)	1(1.9%)	13(3.9%)
Conviction ( public right)	9(12.3%)	11(15.9%)	19(25.3%)	9(14.8%)	6(11.3%)	54(16.3%)
Conviction (public right & Plaintiff waiver)	7(9.6%)	8(11.6%)	8(10.7%)	6(9.8%)	6(11.3%)	35(10.6%)
No Conviction (public right & Plaintiff waiver)	6 (8.2%)	4 (5.8%)	5 (6.7%)	6 (9.8%)	6 (11.3%)	27 (8.2%)
No condemnation (two rights)	27 (37%)	30 (43.5%)	24 (32%)	17 (27.9%)	14 (26.4%)	112 (33.8%)
Compensation *(Death)	9 (12.3%)	5 (7.2%)	7 (9.3)	7 (11.5%)	18 (34%)	46 (13.9)
Compensation *(Disability)	-	5 (7.2%)	9 (12%)	7 (11.5%)	11 (20.8%)	32 (9.7%)
*Other Compensation	38 (52.1%)	29 (42%)	36 (48%)	30 (49.2%)	10 (18.9%)	143 (43.2%)

\* Statistically significant value (<.05)



*Chart 1 :* The trend of the decisions issued within five years

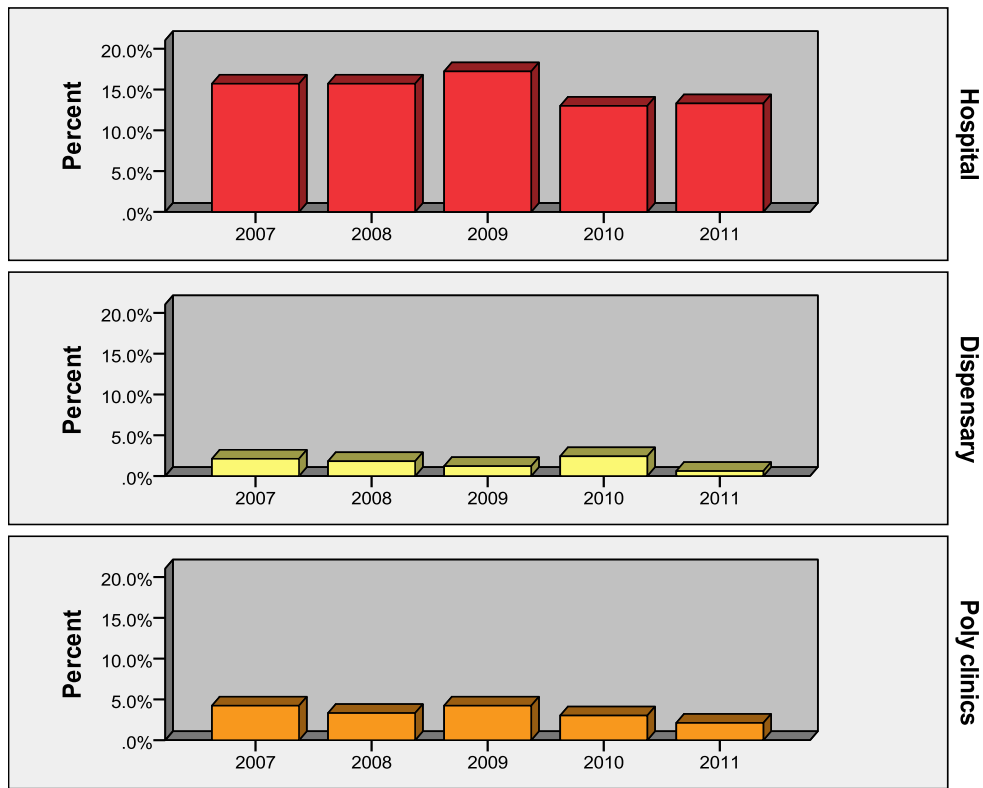


Figure 1 : Percentage of distribution decisions on health facilities

The classification decisions issued on the specialty: obstetrics and gynecology (n = 64, 19.3%), general surgery (n = 48, 14.5%), orthopedics (n = 30, 9.1%), surgical Urology (n = 9, 2.7%), Neurosurgery (n = 14, 4.2%), Ear, Nose and Throat (n = 11, 3.3%), ophthalmology (n = 11, 3.3%), surgical specialties (n = 37, 11.2%), internal medicine (n = 19, 5.7%), anesthesia and intensive care (n = 2, 0.6%), pediatric (n = 30,

9.1%), dental (n = 23, 6.9%) and other disciplines (n = 33, 10%). **Figure [2]** comparison shows the trend of resolutions by specialty for each year. There was high percentage on issued decisions on the Gynecology and Obstetrics and general surgery and statistically significant (< 0.05). The total percentage of the decisions according to all specialties for five years as shows in **Figure [3]**.

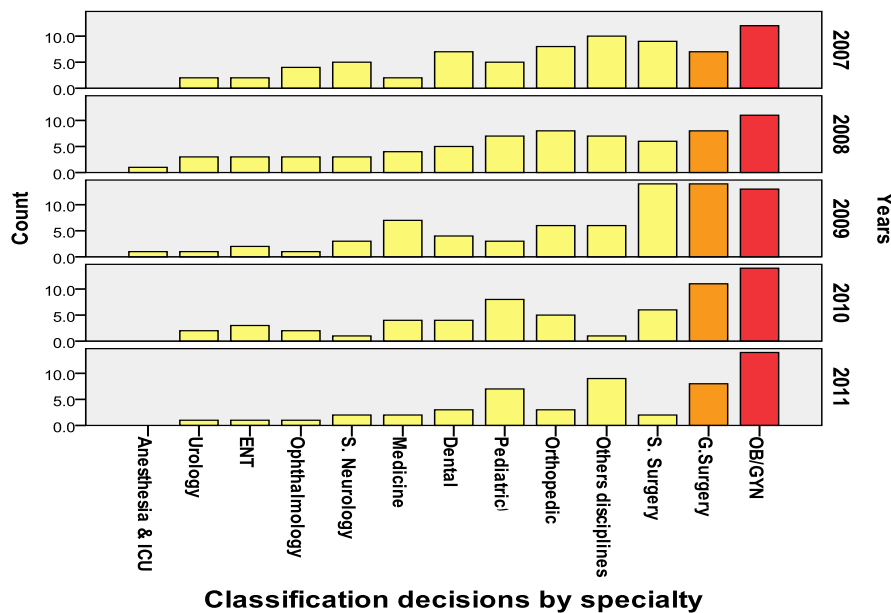


Figure 2 : Classification of decisions by specialty



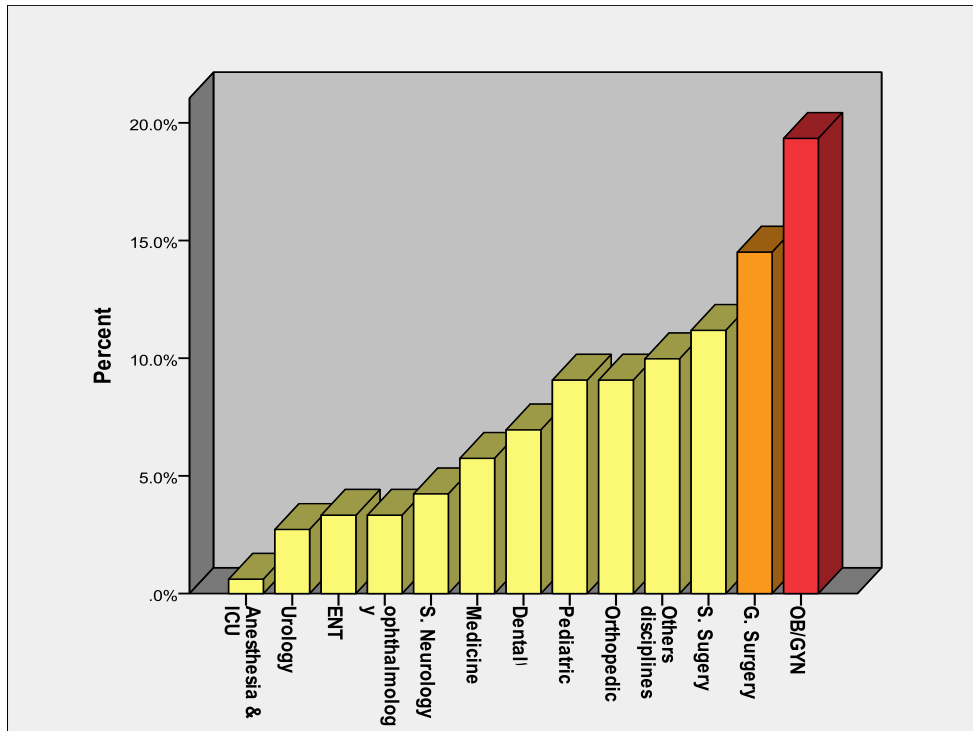


Figure 3: Total percentage of classification decisions by specialty

According to the result of verdicts issued during the five years the highest rate was in 2011 in two rights condemnation and in 2009 the highest condemnation was in the public right as shown in Chart [2]. It should be noted that the overall total percentage of verdicts rate was higher in the public right

compared to the right of plaintiff as shows in Figure [4], and is a statistically significant ( $< 0.05$ ). The cumulative conviction rate in the decisions issued was almost five times fold in 2011 compared to 2007 as shows in Figure [5].

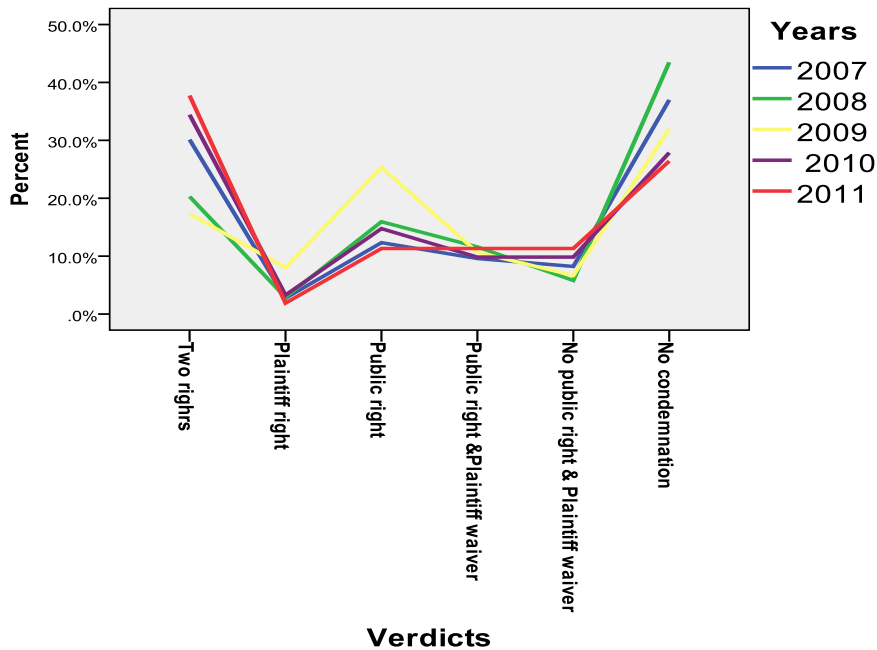


Chart 2: Comparison between the proportion of judgment in decisions during the five years

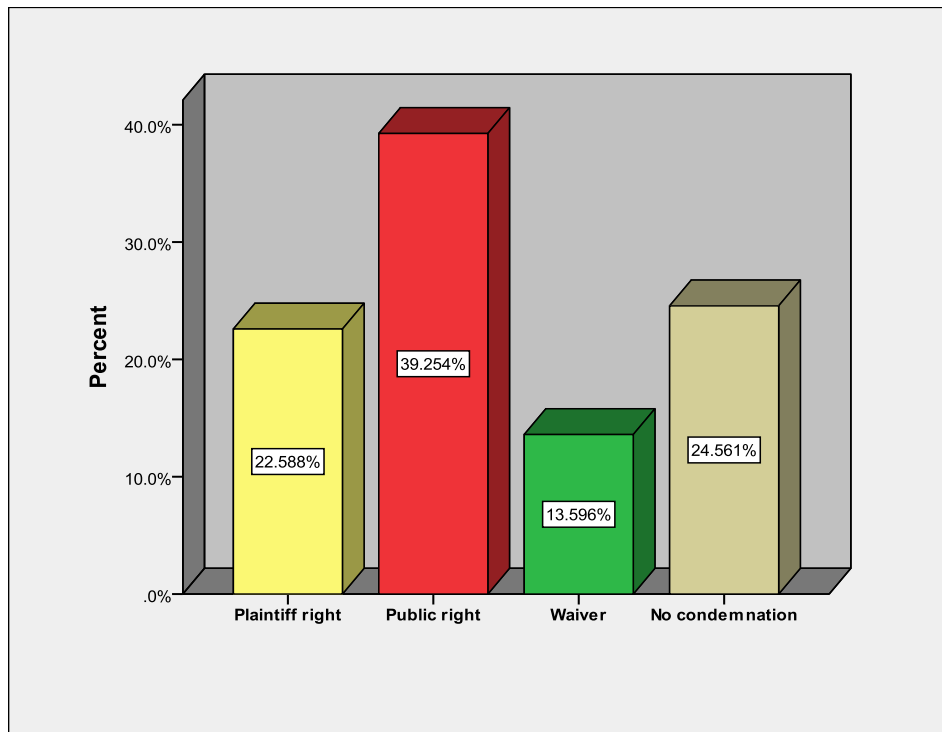


Figure 4 : Total percentage of the verdicts during the five years

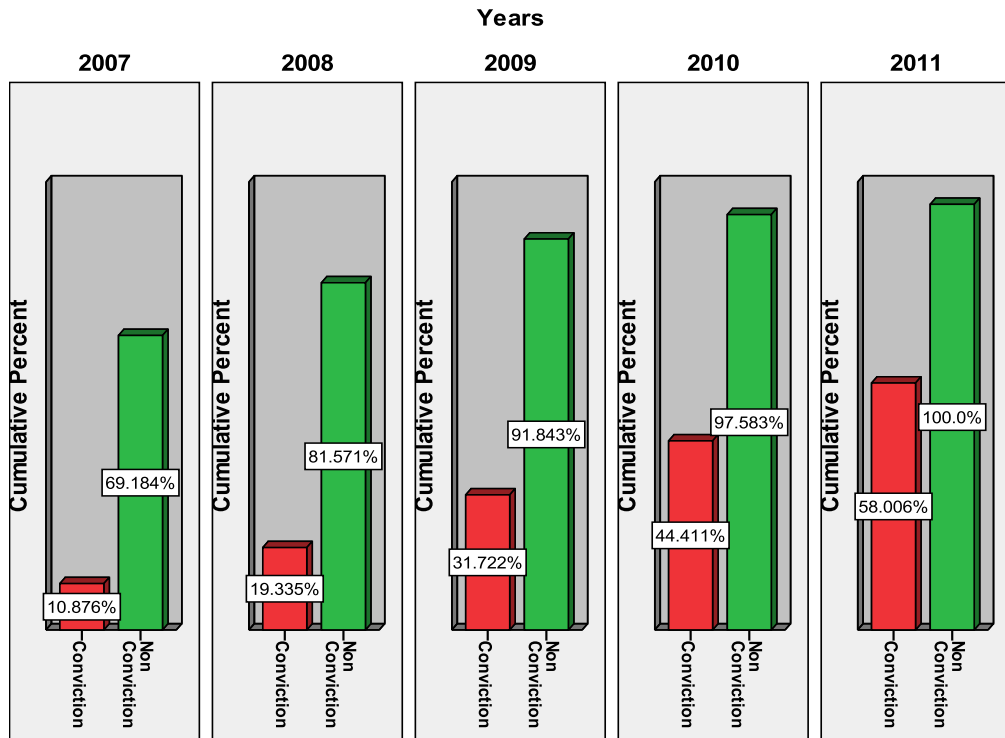


Figure 5 : Cumulative conviction rate in the decisions issued during the five-year

The defendants were total 845 of the health professions during the study period. Chart [3] shows the direction of the highest percentage of defendants from health professions was in 2009. Chart [4] shows the trend rate Convicted (n = 252, 29.8%) compared to non

convicted (n = 593, 70.2%) of the Health Professions at rate (1:3.4) convicted. They classified as follows: Doctors (n = 236, 93.7%), nursing and midwifery (n = 13, 5.2%), technicians (n = 2, 0.8%) and other professionals (n = 1, 0.4%) as shown in Figure [6].



Chart 3 : The trend of defendants proportion of health professions during the five years

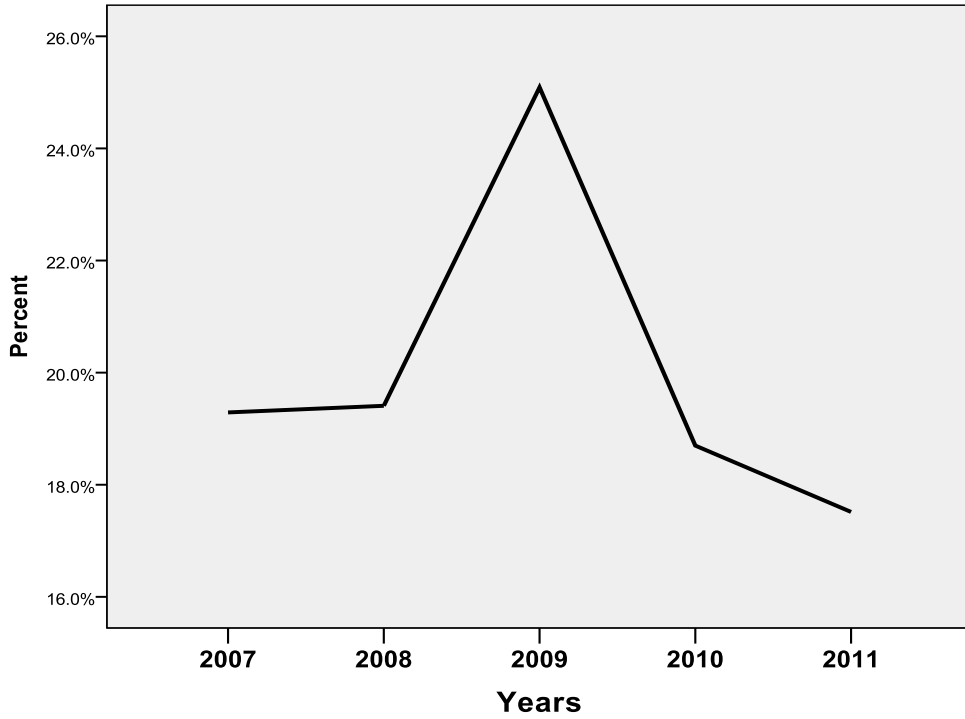
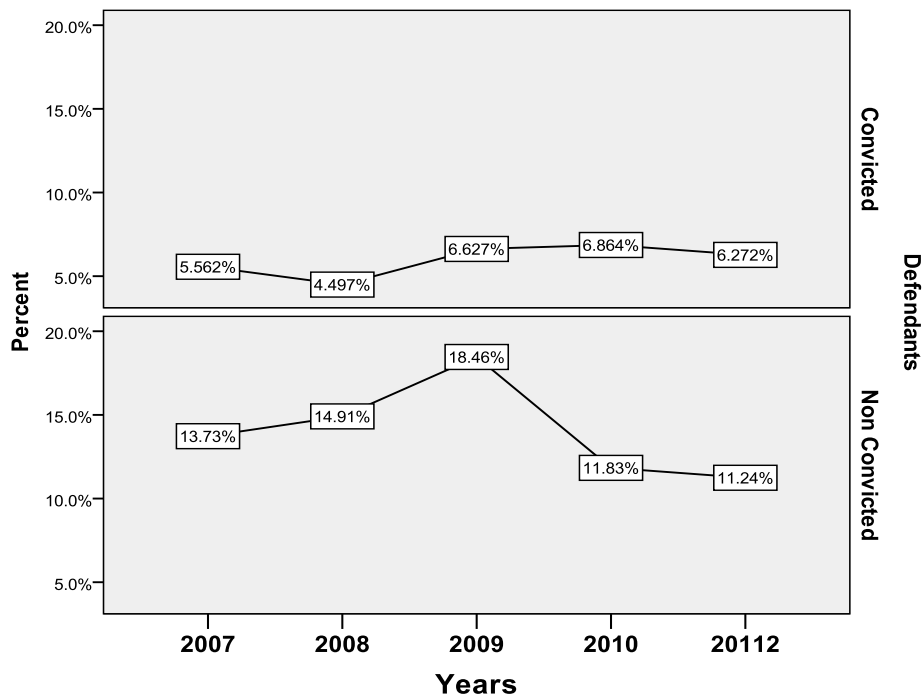


Chart 4 : Comparison between the trend of defendants proportion convicts and non-convicts in medical errors



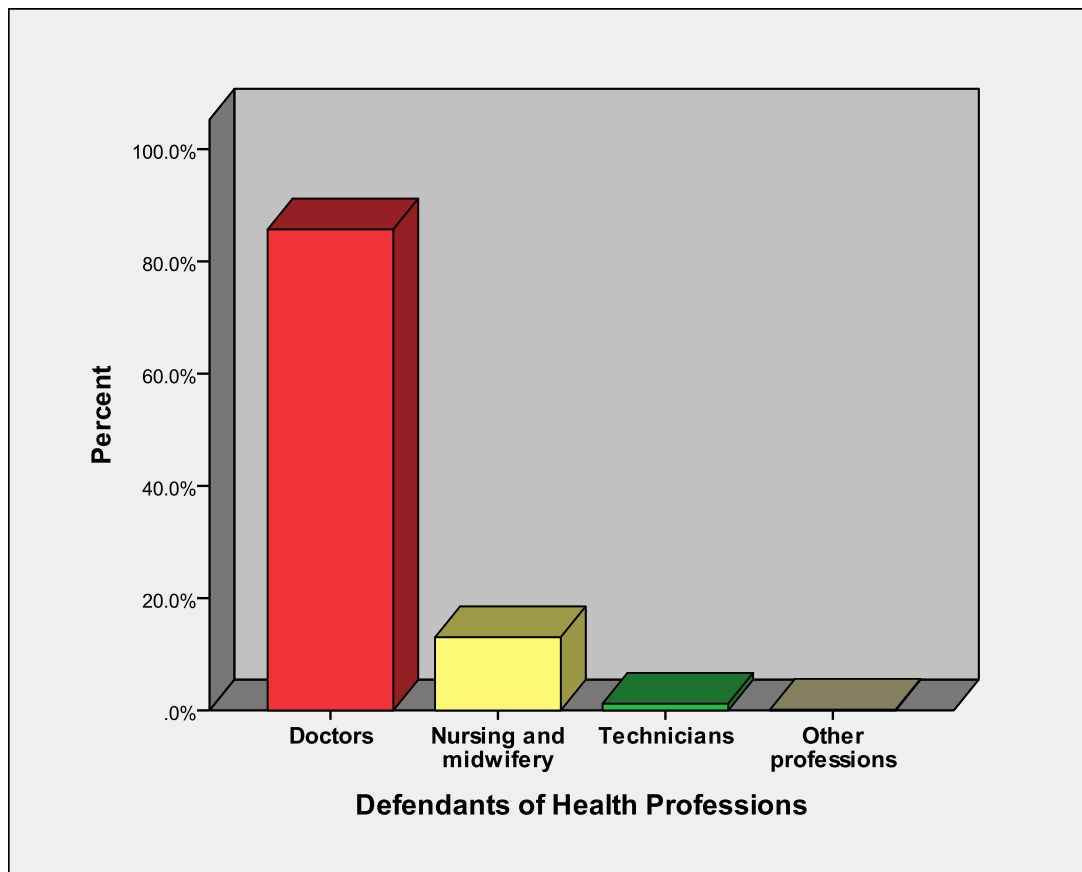


Figure 6 : Total % of Defendants of the health professions within five years

Those doctors were convicted according to the specialty: obstetrics and gynecology (n = 55, 16.6%), general surgery (number = 33, 10%), orthopedics (n = 11, 3.3%), surgical Urology (n = 5, 1.5%), neurosurgeons (n = 7, 2.1%), Ear, Nose and Throat (n = 6, 1.8%), ophthalmology (n = 4, 1.2%), plastic surgery (n = 12, 3.6%), surgical specialties (n = 6, 1.6%), internal medicine (n = 14, 4.2%), anesthesia and intensive care (n = 22, 6.6%), pediatric (n = 26, 7.9%), dental (n = 17, 5.1%), dermatology (n = 1, 0.3%), radiology (n = 3, 0.9%), other disciplines (n = 15, 4.5%), laboratory and blood banks (n = 1, 0.3%). The highest condemnation were against Obstetricians and Gynecologists and general surgery, this is consistent and confirmed with literature studies [5-6]. It should be noted that the trend rate of doctors convicted were high and the non convicted in a decline with an inverse relationship as shown in the chart [5]. The cumulative percentage of convicted doctors compared with non-convicted was more than five times , and statistically significant (< 0.05) as in Figure [7].



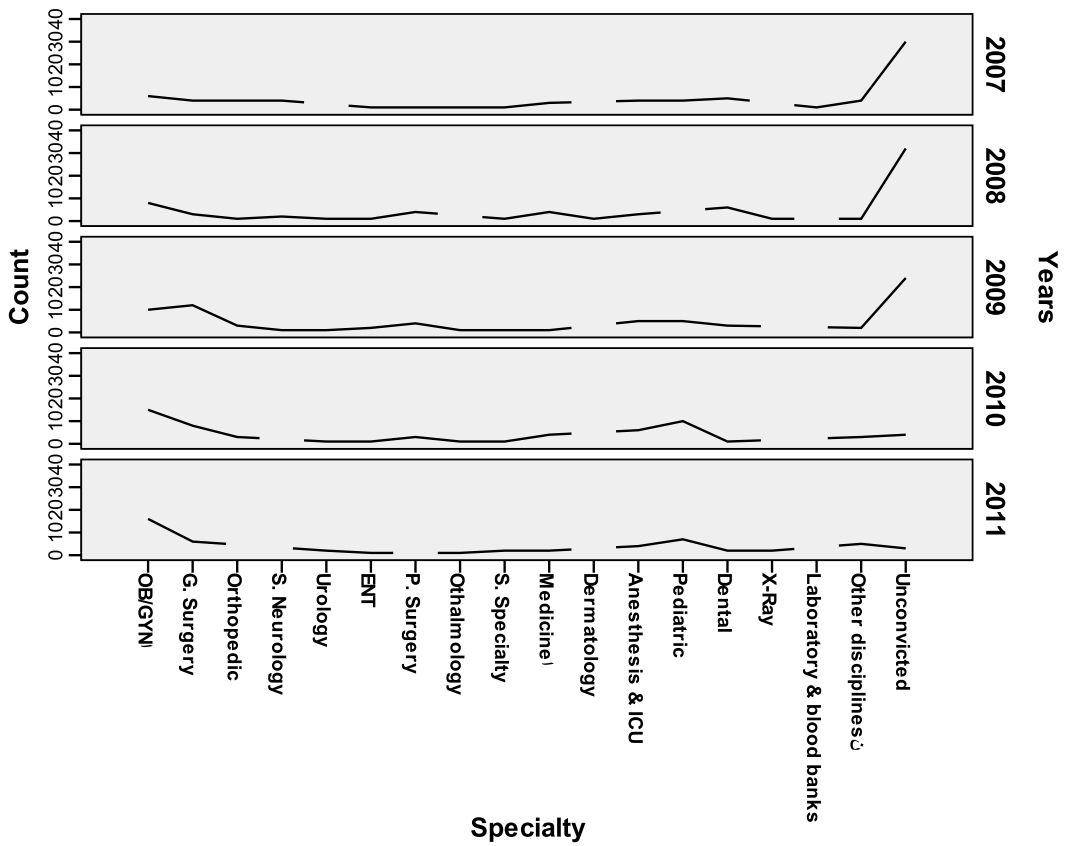


Chart 5: Comparison between the trend number of defendants convicted and non convicted each year

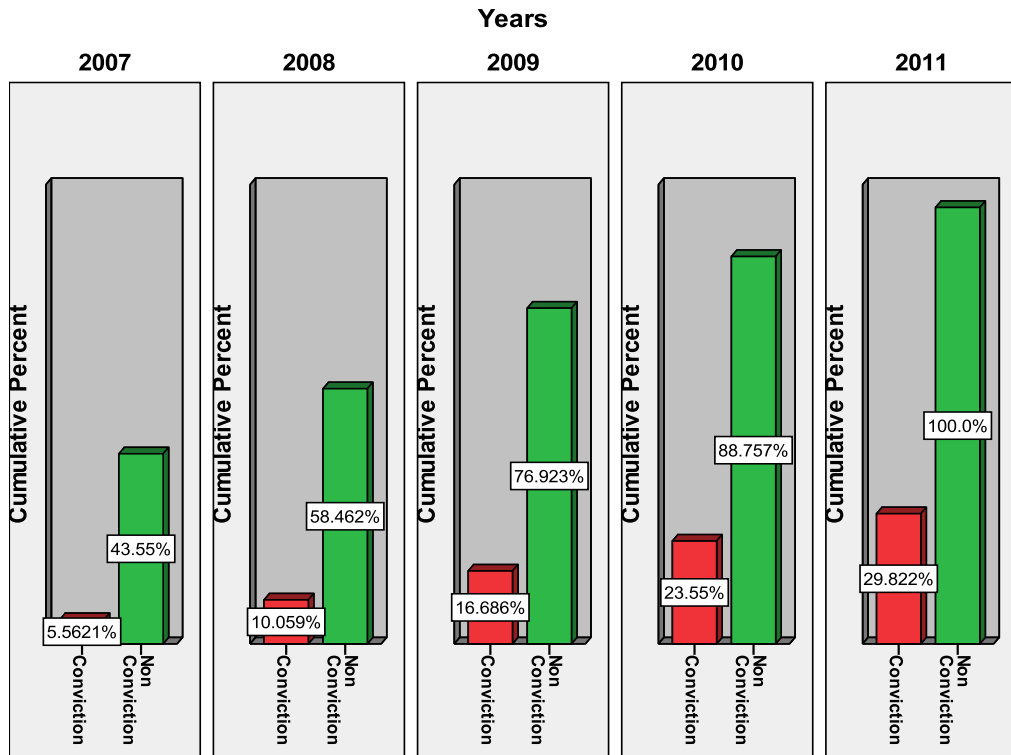


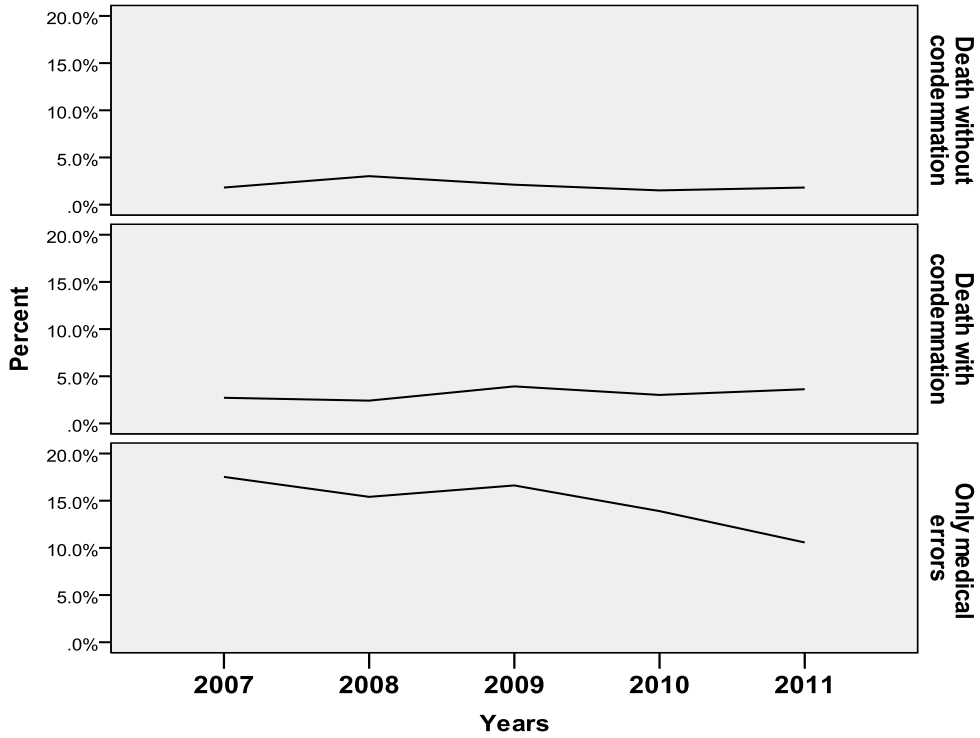
Figure 7: Cumulative percentage clarify the relationship between convicted and non-convicted

The total number of deaths (n = 86, 26%), and the percentage of compensations in the deaths (n = 46, 13.9%) and disability "partial or total loss" as result of medical errors (number = 32, 9.7%) within the five

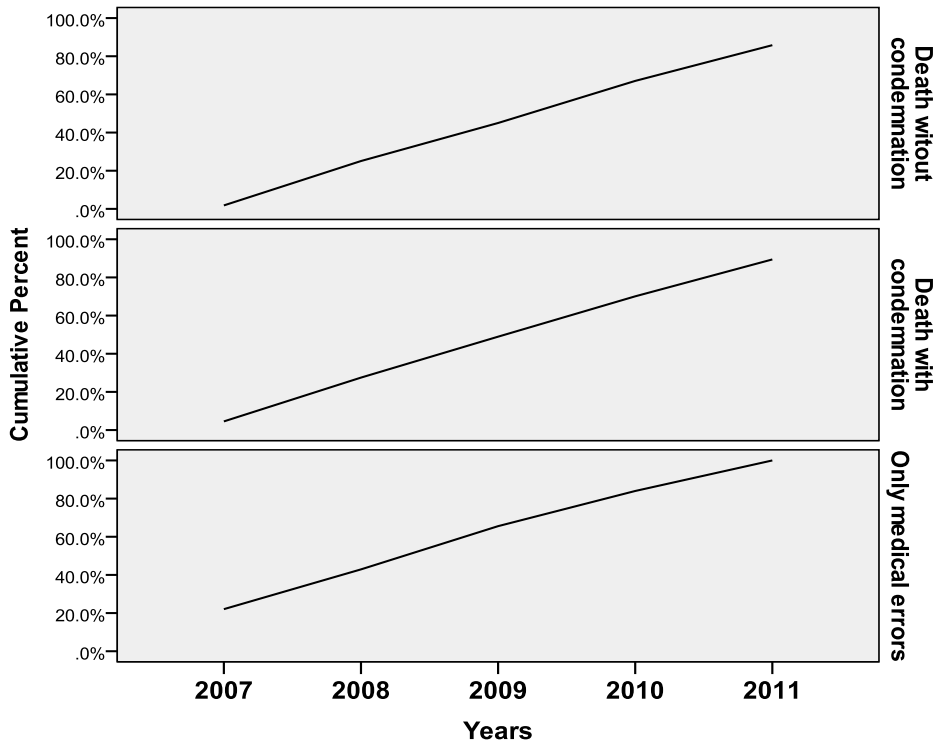
years. Chart [6] shows the trend of medical errors compared with the deaths condemnation and is a statistically significant (< 0.05). The cumulative mortality rate is on the rise from result of medical errors as shows

in **Chart [7]**. In 2011 the percentage of compensation in the deaths and disability were higher compared to other medical errors. This reflects the rise in the amount of the compensation for the plaintiff right in mortality and

disability as a result of medical errors, especially from the beginning of 2010-2011 and is a statistically significant ( $< 0.05$ ) as in the **Figure [8] & Charts [8-9]**, respectively.



*Chart 6 :* Comparison between the number of medical errors and mortality



*Chart 7 :* The cumulative mortality trend as a result of medical errors



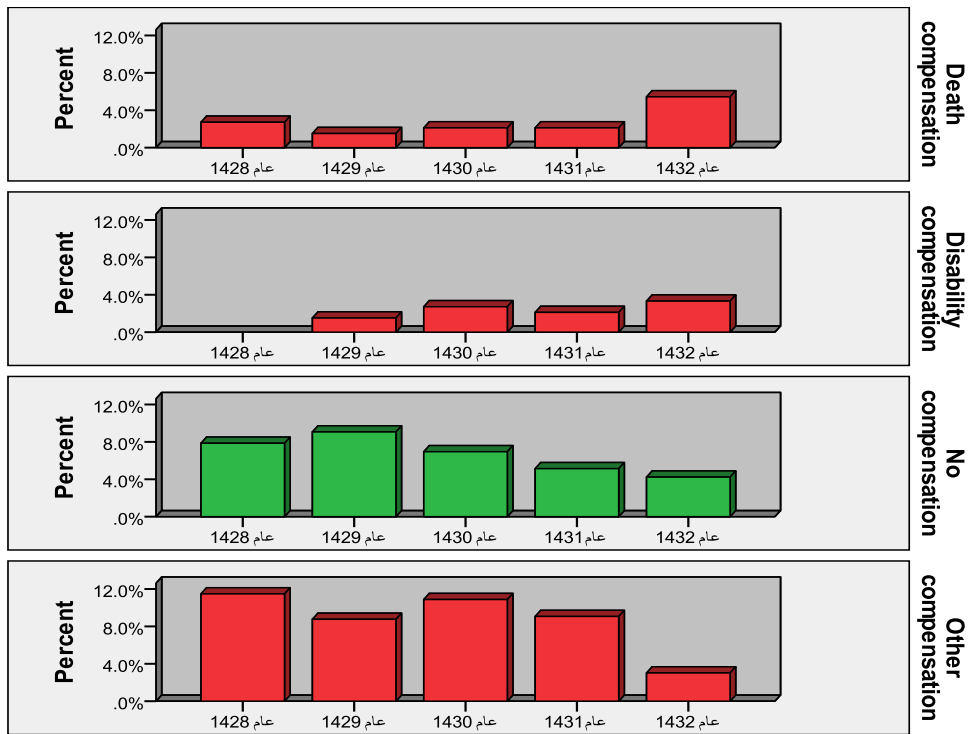


Figure 8 : Comparison between the types of compensation as a result of medical errors

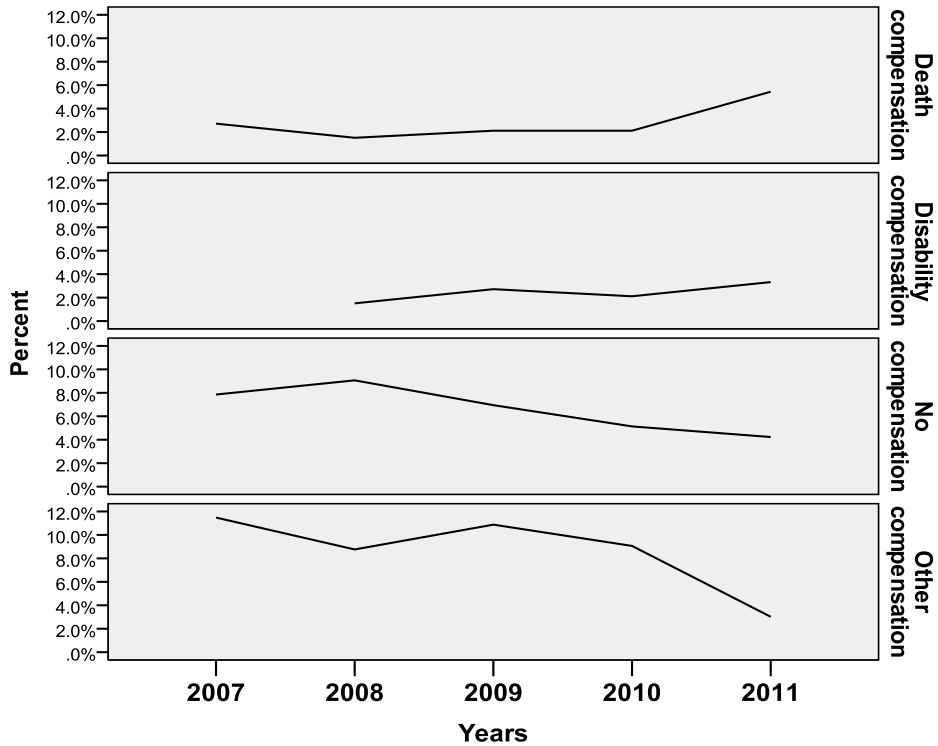


Chart 8 : Comparison between the trend compensation % as a result of medical errors



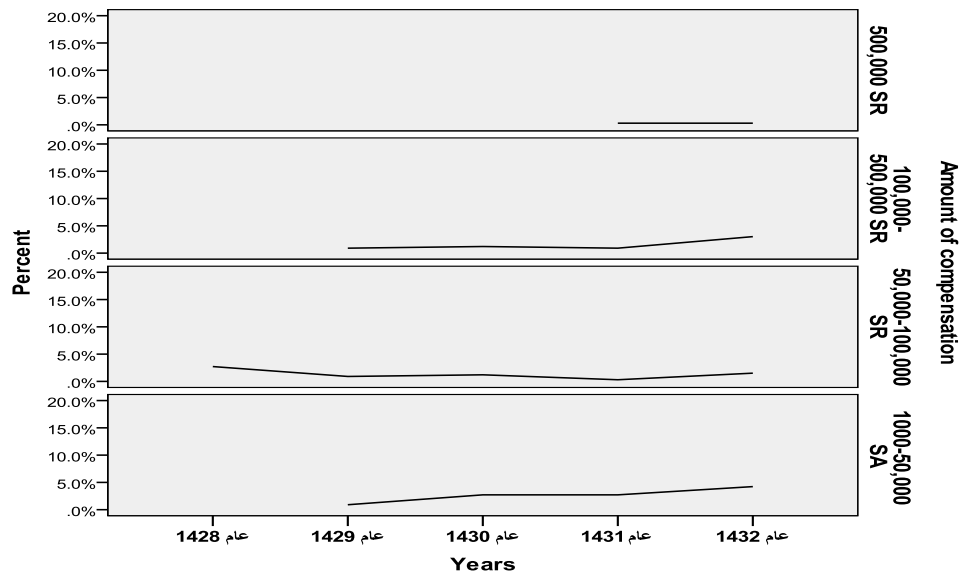


Chart 9 : The trend of amount compensation as a result of medical errors

#### IV. DISCUSSION

Undoubtedly the study and analysis of the issues of the private health sector for medical errors is to consolidate the principle how we are dealing with medical errors in terms of analysis of the reasons and reach the problem for diagnosis. So, it is imperative to know the errors and irregularities to reduce them and educate the health professions on the adverse events in medical practice for purpose to raise the awareness and raise the society's culture of health and participation in the decisions and recommendations to become part of the indicators that help to develop a mechanism to avoid those mistakes and improve the way of medical follow-up and develop solutions necessary and recommendations to the competent health authorities [7-8]. And the follower of this vital sector in particular there are large number of issues and the complaints against the private health facilities [9-10]. So it is necessary to highlight and analyze the decisions and convictions to know the medical errors in the private sector where to? After studying the decisions and judgments and convictions, the total percentage of the public right was greater versus the plaintiff private right. Although the mistakes due to lack or bad of the communication are one of causes, there was lack of patient counseling, the expected complications from the treatment which are recognized medically not explained to the patient and poor documentation [11-12]. Also, the surgical intervention expectation not discussed, lack of follow-up of the medical team or lack of the policies, procedures and systems clear for health facilities care, patient safety and the medical services recognized by profession assets [4]. Failure to enlist the expertise in the difficult cases make the patient at risk and the complications could have been avoided by transfer into centers for which there are

all possibilities of medical cadres specialized health and medical equipment to the crisis [9]. The negligence of such factors was one of the reasons that made high conviction rate in the decisions and the cumulative percentage to more than five times during this study, and statistically significant (< 0.05).

That an Article (27) of the Regulations for practicing health professionals in Saudi Arabia defined the plaintiff private right is "all wrong professional from the doctor or from one of his assistants and the consequent harm to the patient is committed to the committed compensation and the legitimacy of Health Authority board forth in this system the amount of compensation" In the case waive your right, this not mean dropping the public right according to the Regulations for practicing health professionals in Saudi Arabia, but convicted for each violation or out of the doctor in his behavior on the rules and medical recognized assets time when the implementation of the medical work [3,13]. The proportion of waiving plaintiff right and in the presence of condemnation in the public right was 10.6% versus without public condemnation 8.2 through five-years.

That negative behavior in the communication lead to increase the proportion of litigation against doctors, even when there were no negative results, in the year 2009, was the largest proportion of defendants of the health professions and with the rate 1:3.4 convicted during the five years. Also the delay in giving the truth to the patient and his family or treatment failure or refrain from giving the patient a detailed medical report "diagnosis and treatment" is one of the factors that accelerate sued the doctors [9,14]. The orbiter and through of this study that the conviction rate for defendants began to climb (50.7%) from 2008, and until 2009-2011, the conviction rate has not changed and



remained within this percentage (62.3%) as shown in **Table [1]**, and statistically significant ( $< 0.05$ ). where the cumulative percentage for the conviction rate was (30%) in 2011, compared to (5.6%) in 2007 as shown in **Figure [7]**.

This study also showed the proportion of serious medical errors, such as a death or disability as a result of neglect and lack of follow-up and experience or the delay in therapeutic or surgical intervention where the total compensation rate in the deaths were 46 (13.9%) and disability was 32 (9.7%) from partial or total loss functions or permanent disabilities as a result of medical errors. The compensation from disability were three times fold 11 (20.8%) in 2011, compared 5(7.2%) in 2008, and statistically significant ( $< 0.05$ ). This reflects on rising in the amount of the compensations to the plaintiff right for deaths or disability, and especially the beginning of 2010-201 1 as shown in **Table [1]**.

## V. CONCLUSION

The conviction rate in the decisions of the health profession, and especially the doctors in five years is on the rise and thus this is reflected on the trend of medical errors into upward in the private health sector. The highest condemnation were against Obstetricians and Gynecologists and general surgery compared to other disciplines

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## Primary Lymphoma of the Uterine Cervix

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*Hospital Universitario Miguel Servet de Zaragoza*

**Abstract-** Cervical lymphoma is a rare entity that requires differential diagnosis with cervical cancer. Cytology is often insufficient for diagnosis being necessary to perform deep biopsies. There is no standard treatment but most of the treatment rates were based on chemotherapy and/or radiotherapy followed sometimes surgery. We report the case of a patient with non-Hodgkin lymphoma of diffuse large B cell located in the uterine cervix treated with chemotherapy followed by consolidation radiotherapy.

*GJMR-E Classification : NLMC Code: WP 440, QZ 350*



*Strictly as per the compliance and regulations of:*



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# Primary Lymphoma of the Uterine Cervix

José Gutiérrez <sup>α</sup>, Y; Marcuello Franco <sup>σ</sup>, Ac; Lanzón Laga <sup>ρ</sup>, A; Puig Ferrer <sup>ω</sup>, F; Del Agua Arias <sup>¥</sup> & C; Ruiz Conde Ma. <sup>§</sup>

**Abstract-** Cervical lymphoma is a rare entity that requires differential diagnosis with cervical cancer. Cytology is often insufficient for diagnosis being necessary to perform deep biopsies. There is no standard treatment but most of the treatment rates were based on chemotherapy and/or radiotherapy followed sometimes surgery. We report the case of a patient with non-Hodgkin lymphoma of diffuse large B cell located in the uterine cervix treated with chemotherapy followed by consolidation radiotherapy.

## I. INTRODUCTION

Non-Hodgkin's lymphoma is 75% of all lymphomas (1). It is estimated that the incidence in Spain is 10.8 cases per 100.000 women/year, with 2.400 new cases diagnosed per year in women. Ranked seventh in incidence by type of cancer in both men and women, remaining stable in the last years. The likelihood of developing non-Hodgkin lymphoma throughout life is 1 in 51 women.

This disease is found mainly in the lymph nodes or lymphoid tissue and female genital involvement is rare, and can exist in some cases of disseminated disease. The most common gynecologic location is the cervix, followed by uterine corpus and ovaries (2).

Primary cervical lymphoma is an extremely rare entity that presents clinically as cervical cancer, with which we must make a differential diagnosis. Usually presents with vaginal bleeding, dyspareunia and pain. The subtype more frequently described is the large B cells (3).

Diagnosis is often difficult because the cytology may be normal, by originate in the stroma with preservation of the scaly surface, obtaining false negatives so taking deep biopsies for histological confirmation is recommended (4).

In early stages the treatment usually more applied is radiotherapy followed by chemotherapy and/or surgery, but in advanced stages and in cases of genital lymphomas chemotherapy seems the best treatment option (5).

We report the case of a patient diagnosed with non-Hodgkin lymphoma of diffuse large B cell uterine location, with good response to chemotherapy.

## II. CASE REPORT

A 58 year old patient that check in September 2013 per episode of postmenopausal metrorrhagia associated with hypogastric discomfort. As referred only previous bilateral saphenectomy in 2010.

On pelvic examination a bulky tumor that seemed to depend on the posterior lip of cervix showed, this finding was confirmed by ultrasound in which 85mm cervical mass was noted. Given these findings, the following additional tests were requested:

- Pelvic MRI: expansive and infiltrative bulky cervical tumor of 93mm with extension to the uterine body, right parametrium, anterior vaginal wall and dubious infiltration of the rectal wall. Affection of bilateral pelvic and inguinal lymph nodes rights (Figures 1 and 2).

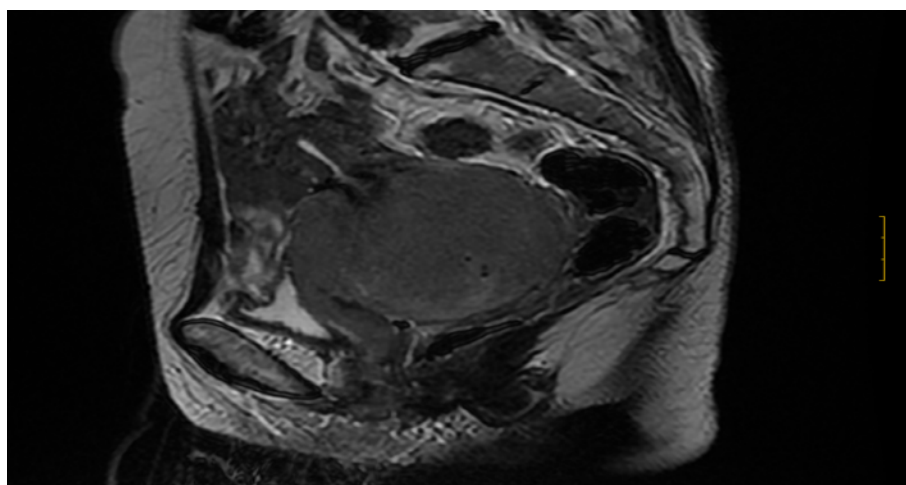


Figure 1 : Cervical mass in the pelvic MRI

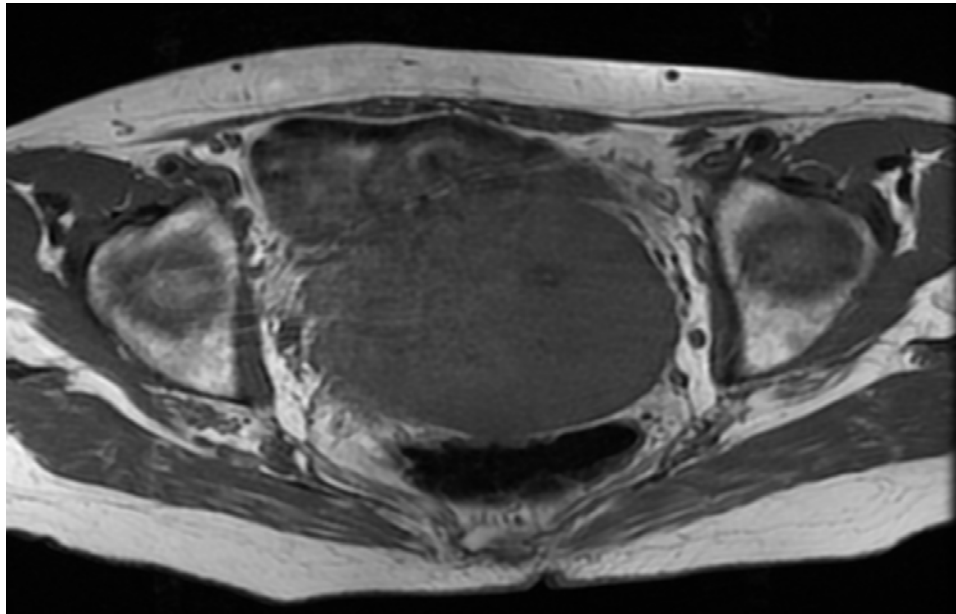


Figure 2 : Cervical mass in the pelvic MRI

- Thoraco-abdomino-pelvic computerized axial tomography (CAT): 95mm tumor in cervical-uterine body with presence of pathologic paraaortic lymph nodes and left iliac path and right inguinal region.

No findings of significance in oncologic thoracic region, absence of axillary and mediastinal lymph nodes (Figure 3).

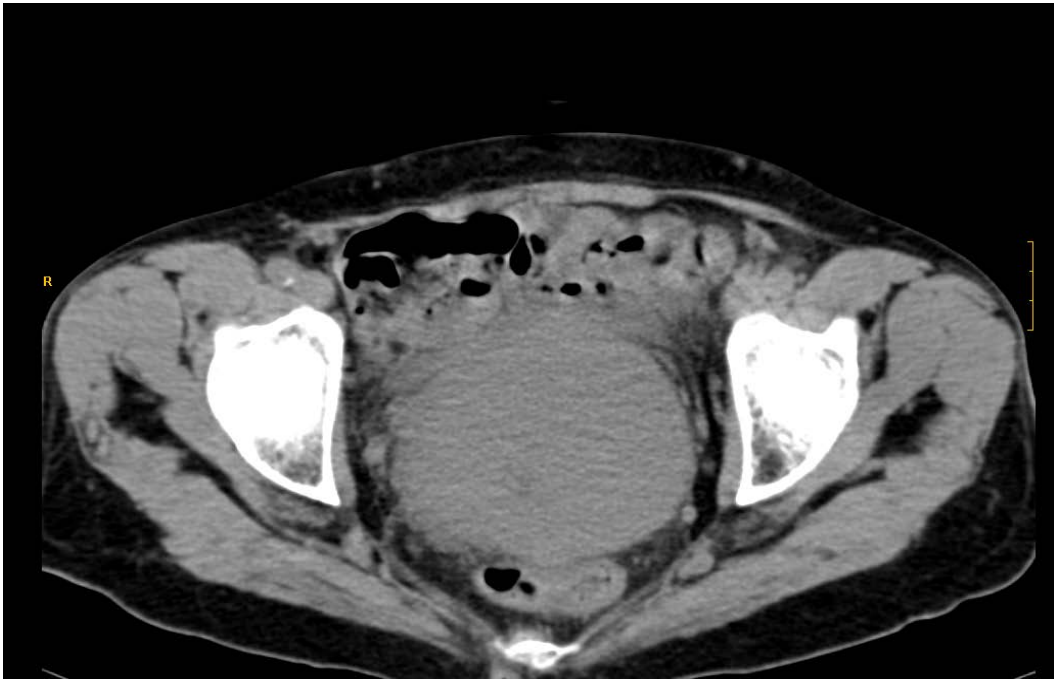


Figure 3 : Pelvic CAT

- Tumor markers: normal.
- Liquid based cervical cytology: negative for intraepithelial lesion or malignancy.
- Automated large-core biopsy of the mass with a 14-gauge needle: diagnosed large cell lymphop-

roliferative process, immunophenotype B. Immunohistochemistry study: bcl2: +, BCL6: +, CD10: -, EMA: -, high Ki67 proliferative index (Figures 4 and 5).



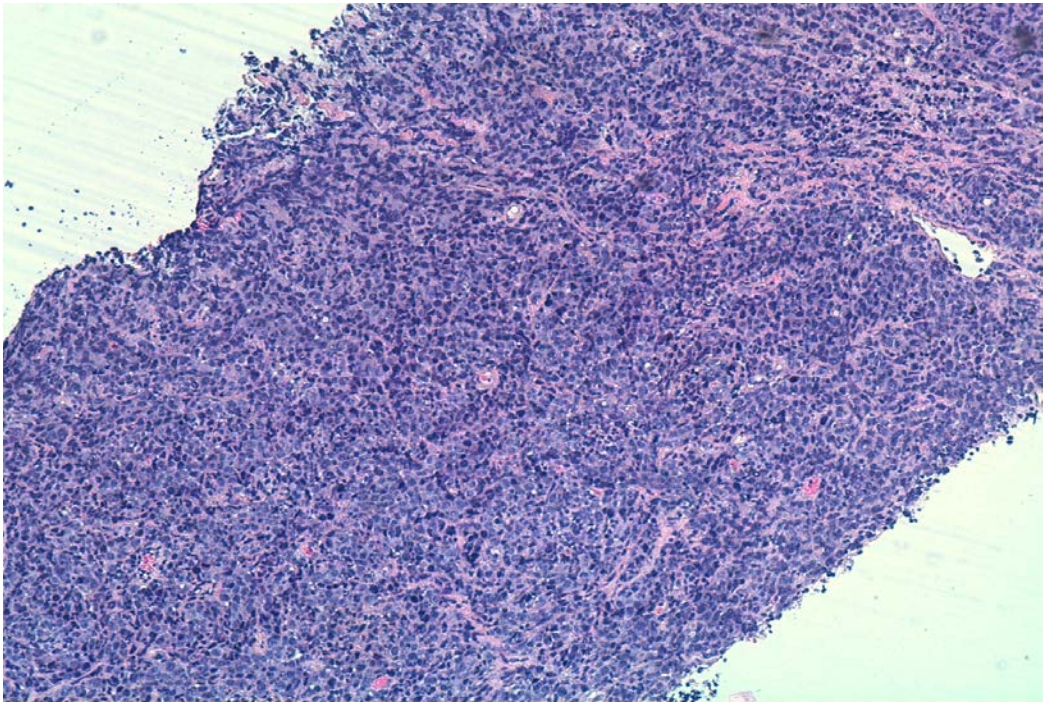


Figure 4 : Histological examination of the tumor: hematoxylin-eosin staining

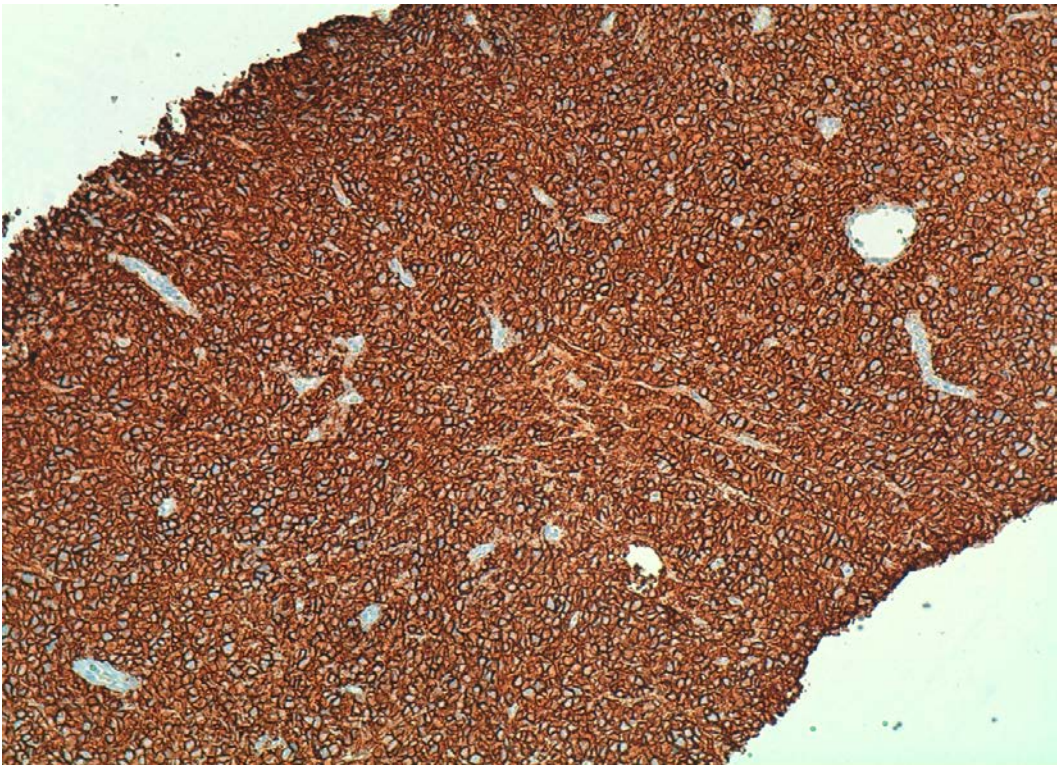


Figure 5 : Immunohistochemistry study: CD20 that identifies the lymphoid phenotype B

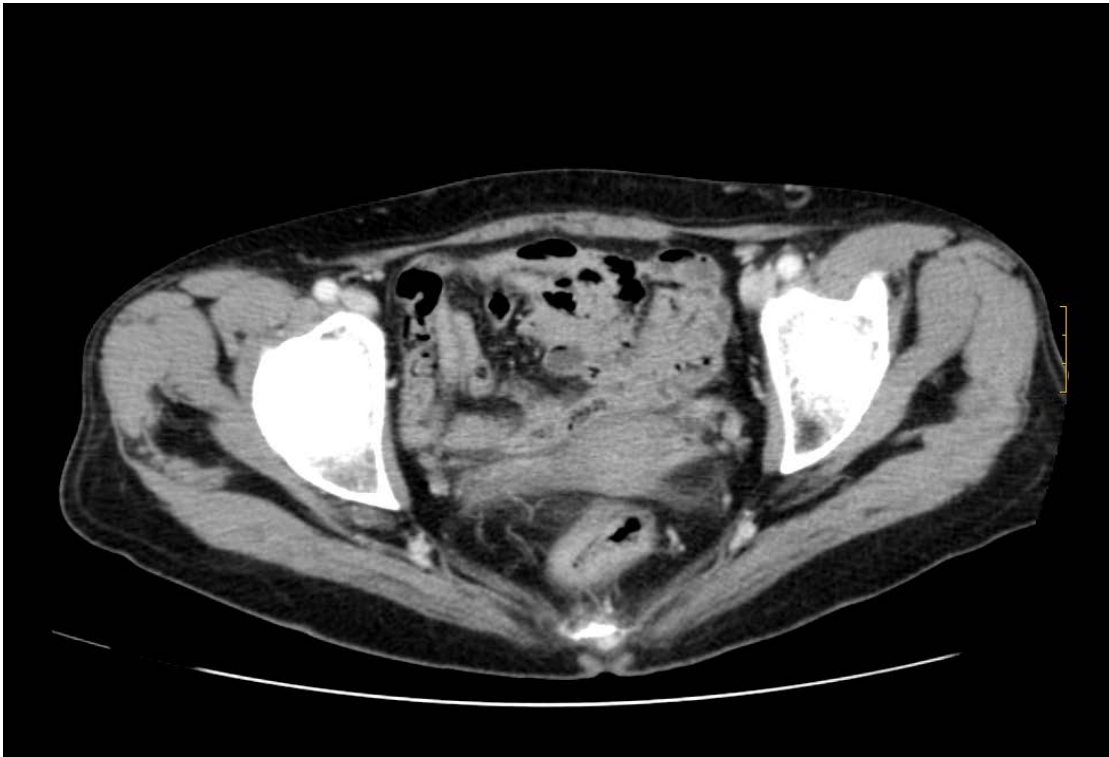
Given the pathological diagnosis proceeded to perform a bone marrow biopsy to rule out involvement of the same, performing a puncture in the right iliac crest with result: bone cylinder normocellular no relevant morphological lesions without signs of atypical lymphocytosis in the material submitted.

After the result of the additional testing and the extension study, was diagnosed with non-Hodgkin lymphoma, diffuse large B cell uterine location. Stage IV, extranodal bulky mass with right parametrial infiltration, not infiltrated bone marrow, two IPI risk factor (R- IPI 2).



With this diagnosis was prescribed R-CHOP-based chemotherapy regimen receiving 6 cycles from 13/10/14 to 04/02/14. The treatment period was uneventful except for an episode in December 2013 of pneumonia requiring admission for 10 days and was resolved with antibiotic, antiviral therapy, oxygen therapy and noninvasive respiratory support, lagging the 4th cycle of chemotherapy only in 10 days.

At the end of chemotherapy CAT was performed again in March 2014 with almost complete regression of the mass of the uterine cervix, without identifying adnexal masses or supraclavicular, axillary or mediastinal lymph nodes (Figure 6). At present the patient is doing consolidation radiotherapy.



*Print 6* : Pelvic CAT after the end of chemotherapy regimen

### III. DISCUSSION

Extranodal lymphomas represent 15% of Non-Hodgkin lymphomas (6). Of these only 1% originates in the genital tract. So there are no large series to define a standardized treatment. The uterine cervix is the most frequent affected of the genital tract (7), as in our case. Over 75% of cases are diagnosed in premenopausal women, with the average age at diagnosis of 40-44 years (8). Our patient was 58 years old at diagnosis, being well above this age.

To consider as primary lymphoma of the genital tract, the disease should be limited to a single location at the time of diagnosis and there should be no involvement of peripheral blood or bone marrow (9), so after the initial diagnosis obtained with biopsy of the cervical mass conducted a study extension including a bone marrow biopsy and thoraco-abdomino-pelvic TAC, also is advisable to perform a thorough physical examination for suspected peripheral lymphadenopathy. The correct pathologic diagnosis involves making deep biopsies and cytology may have false negatives, as refer Gonzalez et al (10).

The treatment of this condition is controversial because it is a very uncommon condition having few cases reported in the literature. In nodal lymphomas, for patients with localized disease, radiotherapy was the first curative approach and continues to be a part of combined modality therapy (11).

Vaughan et al (12) have shown that almost 70% of patients with localized non-hodgkin lymphoma can be cured by radiotherapy alone. However, the high relapse rate outside the radiation field justifies the requirement of chemotherapy in this setting. A systematic review with meta-analysis the dos Santos et al (13) included four trials with a total of 1.796 patients evaluated chemotherapy alone versus chemotherapy plus radiotherapy and concludes that radiotherapy prolongs progression-free survival, with no impact on overall survival. It must be considered an option for patients who cannot tolerate a high dose or prolonged schedule of chemotherapy.

In advanced stages, the treatment of choice is usually chemotherapy. Neoadjuvant chemotherapy seems an appropriate treatment in cases of genital involvement, according Signorelly et al (14),

chemotherapy followed by surgery or not, obtained a complete response in 75 % of cases and 5-year survival 90%. Another proposed treatment is the primary chemotherapy followed by consolidation radiotherapy, Marco Bravo et al (15) reported 2 cases of cervical lymphoma treated with CHOP chemotherapy regimen, followed by radiation therapy with complete remission in both cases without evidence of disease 23 and 70 months, respectively. In our patient, after the assessment session with clinical tumor board, this was the chosen treatment.

In the current era in which the target therapy appear promising, there have been encouraging results with rituximab, a monoclonal antibody directed against the CD20 antigen expressed by most of these tumors (16).

We thought that since it is a disease so rare, further investigation is needed in this regard bringing more cases to know what is the best treatment we can offer these patients.

#### IV. CONCLUSIONS

Primary lymphoma of the uterine cervix is extremely rare entity. Usually require the completion of deep biopsies for correct diagnosis at the high rate of false negative cytology. They have rapid growth and most have more than 4cm at diagnosis. It is recommended that thoraco-abdomino-pelvic CAT and bone marrow biopsy to rule out disseminated disease. The standard treatment has not yet been established but more often in advanced stages and genital involvement chemotherapy is the treatment of choice. Genital lymphomas appear to be less aggressive than nodal lymphomas with high overall survival, especially in early stages

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# Relationship between Premature Rupture of Membranes and Collagen Amount in Chorioamnionic Membranes in Term Pregnancy

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**Abstract- Aim:** Aim of this study is investigate the collagen amounts that have been deposited within the chorioamnionic membranes of term pregnancies by means of electron microscopy.

**Material and Methods:** The study group was made up by 20 women with term pregnancies who were diagnosed with premature rupture of membranes (PROM). Control group consisted of 20 women with term pregnancies who had no leakage of amniotic fluid. Electron microscopy was utilized to assess the collagen amount within the tissue samples which were acquired from the chorioamnionic membranes of the patients.

**Keywords:** *electron microscopy, premature rupture of membranes, pregnancy.*

**GJMR-E Classification :** *NLMC Code: WJ 190*



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# Relationship between Premature Rupture of Membranes and Collagen Amount in Chorioamniotic Membranes in Term Pregnancy

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**Results:** When the control group was compared with the study group, term pregnancies with PROM were found to have statistically lower quantity of collagen within unit area of chorioamniotic membranes (Mean values are respectively  $69.5\% \pm 26.3\%$  vs  $49.60\% \pm 23.44\%$ ;  $p=0.017$ ; 95% confidence interval: 0.14-0.19)

**Conclusion:** Many factors have been implicated in the etiology of PROM. The present study concludes that the decrease in collagen quantity is statistically significant in chorioamniotic membranes of term pregnant women with PROM.

**Keywords:** electron microscopy, premature rupture of membranes, pregnancy.

## I. INTRODUCTION

The fetal membrane (FM) is the membrane surrounding the fetus during gestation and is a structurally soft tissue critical for maintaining a successful pregnancy and delivery (1). The membrane is subjected to applied stresses during pregnancy and must support the bulk loads of the fetus and amniotic fluid as well as tolerate local deformation associated

with fetal movement (1). The intact FM is a bilayer structure composed of both the amnion layer and the choriodecidua layer. The choriodecidua layer is thicker than the amnion layer and is cellular (1). The amnion layer is stiff and strong and only accounts for approximately 20% of the FM thickness (1). However, the amnion layer dominates the mechanical response of the intact FM (1). Rupture of fetal membranes is an event integral to the onset and development of labor at term normal pregnancy. Premature rupture of the fetal membranes (PROM) is defined as the rupture of the amniotic membranes with release of the amniotic fluid more than 1 hour prior to the onset of labor (2). PROM affects approximately 10% of women at term leading to an increased risk of maternal and neonatal infection (2). The mechanisms by which term or preterm fetal membrane weaken and rupture are not completely understood although it has been attributed to cellular apoptosis, extracellular matrix remodeling, and stretch-induced physical weakening of fetal membranes (3-5). Weakening of term FM is not homogeneously distributed across the entire surface, but is more localized to the area that overlies the uterine cervix (3). This physiologic weak zone is present prior to the onset of labor in the third trimester, as demonstrated from studies of term FM from elective, scheduled, unlabored cesarean sections as well as from spontaneous vaginal delivery specimens (3, 6). This area of altered morphology has been further characterized by the same group of researchers to have increased matrix metalloproteinase (MMP) activity and apoptosis (3, 7).

Collagen is a major constituent of the extracellular matrix of amnion and is responsible for its ability to withstand an applied force. Collagen content in preterm amnions with premature rupture of the membranes was significantly lower than that of preterm amnions without premature rupture of the membranes (8). Meinert et al. have also reported collagen fiber disorganization and that hyaluronan may absorb water, with resultant increases in tissue pressure, causing FM separation and weakness (9).

The purpose of this study was to investigate the collagen amounts that have been deposited within the choriodecidua layer of term pregnancies by means of electron microscopy.

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## II. MATERIALS AND METHODS

Patients were recruited for this study with informed consent, using a protocol approved by the institutional review board. The study group was made up by 20 women with term pregnancies (gestational age  $\geq$  37 weeks) who were diagnosed with PROM due to the observation of amniotic fluid pooling on the posterior vaginal wall during sterile speculum examination. On the other hand, control group consisted of 20 women with term pregnancies who had no leakage of amniotic fluid. All of the women were at more than 37 weeks gestation, did not have diabetes, pre-eclampsia, meconium stained liquor or any fetal abnormalities and did not smoke or have an infection.

Because FMs are heterogeneous over their surface in histologic, biochemical, and physical characteristics, and there is a weak zone in the FM overlying the cervix we used methodology that would allow us to determine the exact location and orientation of each cut piece of FM relative to both the placental disk and the "cervical" weak zone (see reference 3 for details). A circular area 10 cm in diameter centered on the weakest point along the tear line was used to define the weak zone of each FM (3). After fixation using 2.5% glutaraldehyde for 48 hours, fragments were washed in phosphate buffer, 0.1 M, pH 7.3, fixed with 1% osmium tetroxide solution. Fixed tissue stained in azure II – methylene blue for light microscopy investigation with Leica DC200 and DCR-RCM (Leica, Wetzlar-Germany). Thin sections were stained with uranyl acetate and lead citrate and then viewed and photographed with high resolution transmission electron microscope (JEOL JEM-1200EX-BIO).

Statistical analysis was performed using SPSS 13.0 software. For comparison of two groups of variables independent t-test, Mann-Whitney U test was used. Calculations were performed on 95% confidence interval. The values obtained, when appropriate mean  $\pm$  standard deviation (range: minimum-maximum) or number (percentage, %) was expressed as.  $p < 0.05$  was considered statistically significant.

## III. RESULTS

The study included a total of 40 cases, PROM proved to be 20 patients in group 1 (study group) and amniotic fluid flow were not proven 20 patients in group 2 (control group) were included. Between study and control groups for age, gravidity, parity, gestational age based on last menstrual period and ultrasonography findings no statistically difference was found. The demographic characteristics of the study and control groups are shown in Table 1.

Physical examination findings like fever, tachycardia, uterine tenderness, foul-smelling vaginal

discharge, leukocytosis, elevated sedimentation rate, elevated serum C-reactive protein levels as the physical findings EMR which suggest intrapartum infection identified more frequently at study group than the control group, although no statistically important differences were found. Physical examination findings of the study and control groups are shown in Table 2.

For the study group collagen ratio in the choriodeciduamembrane per unit area was found to be significantly lower than the control group (mean values  $69.5\% \pm 26.3\%$ ,  $49.60\% \pm 23.44\%$  respectively,  $p = 0.017$ , 95% confidence interval: 0,14 to 0,19).

## IV. DISCUSSION

Membrane rupture appears not to be entirely a result of physical forces alone, since in 10% of term labor and 40% of premature labor membrane rupture occurs before contractions begin (10). PROM is often a complication for many years, although its pathophysiology is still unclear. Spontaneous preterm birth due to preterm labor and PROM is associated with a variety of clinical characteristics. Possible causes include local amniotic membrane defects, vaginal, cervical or intraamniotic infections especially for group B streptococcal colonization, cervical insufficiency, polyhydramnios, multiple pregnancy, placental abruption, placenta previa, trauma, smoking, zinc and copper deficiency.

The mechanical response of the fetal membranes is a combination of the mechanical responses of the individual chorion and amnion components. Topozada et al. showed that the specific contraction causing rupture of membranes was rarely the most forceful contraction that had been experienced up to that time (11). They argued that prior contractions weakened the membrane so that it subsequently gave way with less force (11). Collagen dissociation in the cervical region of the membranes leading up to parturition has been observed and is thought to represent the site of initial rupture (12). Vadillo-Ortega showed that collagen of the amniotic membrane structure was decreased, whereas, with the solubility of collagen was found to increase collagen degradation activity (13). The possibility that PROM is caused by a deficiency of the different collagen types has been investigated (8, 14). Results of gel electrophoresis examination of amniotic membranes with collagen type III / II, III / IV and III / total collagen by ratios of PROM patients were found to be significantly lower other preterm patients (8). Alterations in membrane protease activity may be involved in the formation of this structurally weaker zone which has also been observed in PROM leading to the hypothesis that protease activity may be elevated in PROM membrane (15). Furthermore, it has been shown that non-weak membranes can be

transformed into weak membranes by in vitro incubation with cytokines (16).

Possible strategies for membrane repair or prevention of premature weakening is important for physiology of fetal membrane rupture. Artal demonstrated that membranes placed in pseudo-amniotic fluid become weaker over 24 h but remain unchanged if a mixture of pharmacological enzyme inhibitors is included (17). Harmali et al. have demonstrated improved membrane tensile strength with iatrogenic defects after application of a fibrin sealant, but that the membrane strength remains less than that of unruptured membrane segments (18). Although gross differences in proteolytic activity were not seen when comparing PROM and normal membranes at term it is possible that differences involving individual proteases are being masked. Milwidsky et al. report no general proteolytic differences between amniotic fluid collected from PROM patients and controls and yet a number of

studies report differences when examining specific proteases (19).

## V. CONCLUSION

Premature rupture of membranes often encountered in the practice of obstetrics, which may cause significant maternal and fetal complications, but its etiopathogenesis is not yet completely unresolved. Many factors have been implicated in the etiology of PROM. The most important of these, is the deterioration of the fetal membrane stability. In maintaining the integrity of fetal membranes, the amount of collagen content is vital. The amount of collagen and its content have role for the pathophysiology of PROM. Therefore, the amount and changes in the content of collagen play an important role for pathophysiology of patients with PROM. Investigations to be carried out about the amount and content of collagen in patients at risk for PROM can be focused on the development of treatment methods.

Table 1 : Demographic Characteristics of Study and Control Groups

variables	Study Group (n=20)	Control Group (n=20)	p
Age (year)	24,85±5,47 (18–39)	24,4±4,88 (16–34)	0,986 <sup>b</sup>
Gravidity	2,45±1,95 (1–7)	1,90±0,96 (1–4)	0,699 <sup>b</sup>
Parity	0,80±0,95 (0–3)	0,50±0,60 (0–2)	0,403 <sup>b</sup>
Gestational age for LMP (week)	38,82±1,42 (36–40,6)	39,64±0,69 (38,3–40,5)	0,390 <sup>b</sup>
Gestational age for USG (week)	37,59±1,041 (35–40)	37,56±1,06 (36–40,3)	0,392 <sup>b</sup>
Cigarette smoking (%)			
yes	2 (%66,7)	1 (%33,3)	0,500 <sup>a</sup>
no	18 (%48,6)	19 (%51,4)	

LMP: last menstrual period, USG: Ultrasound

<sup>a</sup>Fisher's exact chi-square test. <sup>b</sup>Mann-Whitney-U test.

Table 2 : Physical Examination Findings related to the study and control groups

	Study Group (n=20)	Control Group (n=20)	p
Uterine tenderness			
yes	1 (%100)	-	0,500 <sup>a</sup>
no	19 (%48,7)	20 (%51,3)	
Foul smelling vaginal discharge			
yes	1 (%100)	-	0,500 <sup>a</sup>
no	19 (%48,7)	20 (%51,3)	
Body temperature (°C)	36,52±0,35 (36–37)	36,41±0,30 (36–37)	0,282 <sup>b</sup>
Pulse rate (beat/min)	96,80±19,52 (72–146)	91,55±18,22 (66–140)	0,455 <sup>b</sup>
White blood cell count (/dL)	12475,5±2806,6 (7080–19200)	11727±2934,5 (8080–21910)	0,208 <sup>b</sup>
Erythrocyte sedimentation rate (mm/hour)	33,8±15,91 (19–80)	26,9±9,18 (16–53)	0,112 <sup>b</sup>
C-reactive protein (ng/ml)	33,6±36,64 (0–96)	32,4±30,68 (0–96)	0,699 <sup>b</sup>

<sup>a</sup>Fisher's exact chi-square test. <sup>b</sup>Mann-Whitney-U test.

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# Cervical Length and Progesterone: Contribution of Ultrasonography to Decide to Whom Administer the Progesterone

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*Abstract- Introduction:* Preterm birth is considered a worldwide problem having multifactorial causes showing a high rate of morbidity and mortality, even in this 21st century; researchers are working in the proteomics field searching for new solutions to its prophylaxis.

*Objective:* This article is aimed at reaching a review of the most recent aspects concerning the use of progesterone to the specialists who follow up pregnant women having short cervix and history of preterm births.

*Keywords:* cervicometry, progesterone, preterm birth.

*GJMR-E Classification :* NLMC Code: WN 208



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**Abstract- Introduction:** Preterm birth is considered a worldwide problem having multifactorial causes showing a high rate of morbidity and mortality, even in this 21<sup>st</sup> century; researchers are working in the proteomics field searching for new solutions to its prophylaxis.

**Objective:** This article is aimed at reaching a review of the most recent aspects concerning the use of progesterone to the specialists who follow up pregnant women having short cervix and history of preterm births.

**Development:** A transvaginal cervicometry is performed in the 18<sup>th</sup> and 24<sup>th</sup> weeks of gestation, which can also be performed trans-abdominally to determine the length of cervix, the internal cervical os(ICO), the existence or not of cervical funneling, the presence of complete, partial or non-presence of mucous plug, and if sludge is observed in the amniotic fluid or the so-called muddy fluid; in this case, a cervix length lesser than 25 millimeters, in a single pregnancy, helps us to predict a high risk of preterm birth, worsening if the other factors mentioned before are observed; which can be previously explored using this technique. Henceforth, considering these results and evidences, the treatment with progesterone can be established following the recommended scheme.

**Conclusions:** The cervicometry and the assessment of other factors in the cervix, together with the evidences found aid establishing prophylactic measures to avoid preterm births using progestins.

**Keywords:** cervicometry, progesterone, preterm birth.

## I. INTRODUCTION

According to WHO the birth of 130 millions of infants are expected in a year, and thirteen (13) millions will be preterm births approximately, of them 68% die in the fetal component and 70% die in the first week of life and those surviving (50%) will suffer from neurological problems and by 26% learning disabilities. Regarding these figures, there are no doubts about, that preterm birth was in the last and it is still a health problem in this current century<sup>1</sup>.

With the purpose of explaining and solving this difficult problem worldwide, a number of factors that are linked to a higher risk of a preterm birth have been identified: uterine overdistension, vascular factors, and infections, hormonal disorders, immunological, genetic and cervical; by 40-50% of idiopathic causes, it is true

that all these factors, one way or another, can lead to the causes, it is written and proved that to maintain pregnancy the mechanical power of cervix is always necessary, as it provides a barrier between the inferior genital tract and the intrauterine space<sup>2</sup>.

Increase of interleukins secretion and nitric oxide (NO) in vaginal secretions have been reported, which are associated with preterm birth, since these mediators stimulate the apoptosis, the activation of proteases and as a result the disintegration of collagen fibers which leads to a shortening of cervix<sup>3</sup>.

In consequence, preterm birth is defined as an entity having multifactorial causes that can be a trigger for the early maturing of the physiological processes, normally occurring at the end of pregnancy, as a result, cervical alterations before the end of pregnancy could predict a third part of patients with preterm birth<sup>3</sup>.

In consequence, a conclusion can be stated; the risk of prematurity is inversely proportionate to the length of cervix, but a modified cervix is another one link in the sequence of risk factors which determine the preterm birth<sup>4</sup>.

The cervicometry is valid as a screening for a preterm birth, but it is only justified in a population at risk, where the competence of a *sharp-eyed* observer can be taken into consideration as well as the control of quality of the equipments; this then, is the only way to find an answer to this complex health problem<sup>5</sup>.

There are many ways to prevent preterm births and they can vary depending on the case, and on important antecedents such as cervical conization, associated diseases and if it is a single or a multiple pregnancy. But in this review article we are trying to provide an outlook on how cervicometry and the use of progesterone can contribute to the prevention of preterm births.

## II. DEVELOPMENT

Prematurity is still the great problem of the 21<sup>st</sup> century, as a consequence researches related to proteomic are in increase into the first world, which are aimed at finding protein biomarkers that could foresee the possible pathogenesis<sup>5,6</sup>.

These protein biomarkers aid us to determine the possible preterm birth that can include predictable

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and valuable factors to determine its onset, which will then imply demographic causes, personal behaviors along with the findings in physical examinations. These basic sources, to carry out proteomic study, as the searching for these biomarkers are basically found in

plasma, placenta and amniotic fluid (Fig.1). Proteomic has developed new pathways in the knowledge of preterm birth pathogenesis, regarding inflammatory and hemorrhagic patterns, when they are not as well present<sup>6</sup>.

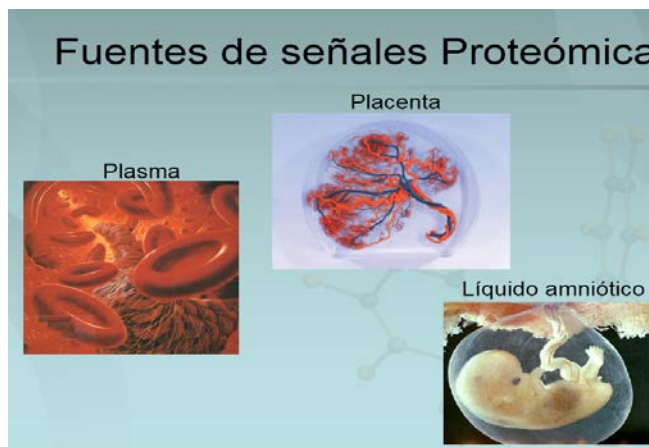


Figure 1 : Images of sources with the proteomic signals are shown: plasma, placenta and the amniotic fluid

Until the researches comprising these markers end, doctors of medicine involve with the treatment of pregnant women must learn very well the points previously proved in recent studies, this way the ultrasonography of the cervix plays its role, therefore between the 18<sup>th</sup>-24<sup>th</sup> weeks of gestation an assessment of the cervix is recommended.

Other different features of the cervix can be assessed, and will be shown in this article, even though it is demonstrated that a short cervix with small amount of mucous plug and *sludge*-amniotic fluid (*muddy*), can be particularly important to identify the pregnant women who are destined to have a preterm delivery<sup>7</sup>.

The *sludge* is the immune response of the organism as protection before a microbial invasion in the internal environment; the microorganisms find different ways of protection, one of them has been defined as the introduction of polyhedral compounds, known as biofilms. The bacteria can stay viable within these structures and the leukocytes penetrate inside them; which has been proved in vitro; however, they are not able to phagocytize the microorganisms there<sup>7-9</sup>.

### III. INDICATIONS FOR THE CERVICOMETRY<sup>5, 10-12</sup>

There are different indications to perform a cervicometry that not only can be reduced to measure the cervix; other variables can also be observed, which will be subsequently discuss.

### IV. AMONG THE MAIN INDICATIONS FOR THE CERVICOMETRY

Previous preterm delivery, which is considered the most important.

1. A patient having a cervical conization.
2. A multiple pregnancy.
3. Repeated artificial abortions.
4. Uterine malformation.
5. Bleeding on the second half of pregnancy.
6. Worrying socio- hygienic conditions.

It is known that a history of preterm delivery predisposes to 20% of repetition in another pregnancy with a precedent of presenting a two-fold increase of probability of its occurrence; but when a delivery takes place before the full-term pregnancy and another at full-term, it is an intermediate risk.

A multiple pregnancy constitutes one of the causes for the increase of preterm deliveries, as a result of the medical development; the use of fertility medications, where the stimulators of ovulation get involved, along with the assisted reproduction, which favors the onset of its presentation, and therefore between 3-6 times more frequent<sup>12,13</sup>.

It is said, nowadays, that as the single pregnancies increase preterm deliveries in 61%, multiple ones make 168% and even in 615% when there are 3 or more products of conception. In equal respects, it is said that 30-50% of the multiple pregnancies and 75% of triplets, come from not so young infertile women treated to procreate, which is considered another element of risk. In some regions of the world, up to 56% of multiple pregnancies were delivered before full term<sup>13, 14</sup>.

### V. VARIABLES TO BE CONSIDERED IN THE ASSESSMENT OF CERVIX (SEE FIG. 2)

The majority of the authors suggest a transvaginal examination of the cervix, because of the

advantage of avoiding the artifacts provoked by the entrance of the sound in the skin to approach to the cervix, keeping away the inconvenient that trans-abdominal ultrasound has, where the bladder must be full of urine, though not as much, because the measures could be distorted when exerting pressure on the cervix, in lengthening it, it does not happen by using transvaginal ultrasound, where full urinary bladder-preparation is not necessary and the transducer approaches the cervix and measures it, along with the rest of the examination performed with better definition<sup>15,16</sup>.

Then, in this examination we can make the measures of the cervix to find out its length, assessment of the internal cervical os, the existence of funneling, where the length is measured and the presence of this last element may be calculated from the internal cervical os (ICO), which requires at least 5 mm dilatation of this funnel-like, with a vertex in the cervical canal. The amplitude of the tunnel corresponds with the dilatation of the ICO and it is possible to measure the functional length of the cervix, measuring the total length of the cervix and subtracting the funneling part, whether the presence or not of *sludge* in the amniotic fluid<sup>15</sup> can be observed from the echographic point of view, and where this definition indicates the presence of a dense aggregate of floating particles in the amniotic fluid, so close to the ICO, as a sign of invasion of microorganisms in the internal environment, generally composed of mucous slug portions, cervical epithelium, fragments of chorion-amniotic membranes, considered as an immune response of the organism before a microbial invasion<sup>7,8,17</sup>, where cells from numerous structures participate: amnion, chorion, deciduas, neutrophils, macrophages, trophoblasts and taking them as germ-free.

During the examination of the cervix, whether the mucous plug is or it is not complete is also explored, which constitutes a well-established structure to protect the internal environment, which is basically composed by water together with organic and inorganic compounds. When the cervical length is reduced, it turns into a small and short slug, almost surpassing its internal and external extremes, this way it loses the protective function and can be easily associated with subclinical infections<sup>10, 11</sup> and for few supporters, the measurement of cervical volume with 3D-echography.

It must be considered that the cervix is an important biomechanical structure to maintain the balance with the uterine body to provide the chronologic end of pregnancy. The majority of the studies suggest that this measure progressively decreases as the pregnancy develops; others, that it increases; and another third part thinks, it has no changes, but the trend of acceptance indicates that its length shortens<sup>10, 12</sup>.

During pregnancy, although normally, the cervix measures 3-5 cm, placing 35 mm in 50 percentile, as much during the second trimester as at the beginning of the third, it has been demonstrated that, for the third months of pregnancy, the elongation of the isthmus starts occurs, helping to differentiate the structures, so that, by the fifth months, delimitations of the inferior segment and the cervix become evident; having a very great importance to interpret echographic images accurately<sup>17-19</sup>.



Figure 2: Echographic images to examine the cervix: length, presence of mucous plug, cervical internal os, funneling and the presence or not of *sludge* in the amniotic fluid.

### VI. ADVANTAGES OF CERVICOMETRY <sup>8,20</sup>

Concerning the data previously exposed it will be necessary to perform a cervicometry having the following advantages.

- It:
1. helps to reduce false positives which are causes of admissions in hospitals.
  2. shortens hospital stays.
  3. reduces the iatrogenic tocolysis.
  4. helps to identify patients having a true need of cervical cerclage.
  5. makes possible the screening of a group of asymptomatic pregnant women with high risk of preterm birth without other evident risk factors.

### VII. INCISION-POINT OF THE CERVICAL LENGTH TO PREVENT PRETERM DELIVERY <sup>10,12,21,22</sup>

With the practice of cervicometry and the advantages it has, adding this is not an invasive technique; incision-point of the cervical length should be determined to carry out the screening for preterm delivery, where the majority of the authors affirm the following conclusions:

1. To use an incision-point for a cervical length of 25 mm to identify preterm delivery in a single fetus during the 2<sup>nd</sup> trimester of pregnancy, starting it at the 20 weeks.
2. To use the measure of the incision-point for a cervical length of 20 mm to screen the possible anticipation of a multiple pregnancy, considering that during the third trimester a marked decrease of 10 mm takes place.
3. To use the measures of incision-point for a cervical length of 15 mm in patients with evident clinical risk of preterm delivery to establish this diagnosis.

It has been proved that, the length of the cervix between the 18<sup>th</sup> and 24<sup>th</sup> weeks of pregnancy lesser than 25 mm and prior to 32<sup>nd</sup> week, pregnant women have a six-fold increase in preterm birth, in relation to pregnant women having a cervix length over the 75 percentile<sup>23,24</sup>.

Then, a cervicometry is performed in a twin pregnancy at 20<sup>th</sup> week approximately; an incision-point of 23 mm seems to establish a population at risk with an increase of preterm delivery-probability<sup>25,26</sup>.

The findings of a short cervix not always results in cervical incompetence or preterm delivery and the length of the cervix must be assessed as a screening in patients at risk.



## VIII. PROGESTERONE ADMINISTRATION AND ITS INDICATIONS

If it is known that one or more previous preterm deliveries, in present pregnancy this condition exists because a short cervix is observed, then it is feasible to administer progesterone supplementation in this patient, which is available of a pharmacotherapy since 1934 and it has been in use for different gynecological diseases, such as: menstrual disorders, infertility, recurrent abortions and other complains<sup>27</sup>.

Progesterone can be found as synthetic and natural progestins or micronized and improved with better bioavailability as oral, vaginal and intramuscular (17  $\alpha$ -hydroxyprogesterone), the last two presentations are the most employed all over the world<sup>27, 28</sup>.

As progesterone can be administered to prevent preterm delivery, it is time to question which the possible mechanisms of actions are<sup>29</sup>:

- ❖ It blocks the oxytocic effect of F2 $\alpha$ -prostaglandin.
- ❖ It avoids the development of gap unions that are formed by two hemi-channels inserted between two contiguous cells where the lumen of one of them continues with the other allowing, when they open, the passage of ions from cytoplasm to cytoplasm of the adjoining cell makes possible the electric synapses without chemical messengers.
- ❖ It blocks the prostaglandins that induce the contractions.
- ❖ It relaxes the smooth myometrium-musculature.
- ❖ It is a suppressant of the action of calcium-calmodulin in the system of kinases diminishing the influx of calcium. It should be remembered that, the calmodulin is an intracellular protein which is one of the regulators in the transduction of the signal of calcium in the cell; besides it intervenes in other metabolic processes.

Other individual and meta-analyses studies sustain the administration of intramuscular 17  $\alpha$ -hydroxyprogesterone (17  $\alpha$  OH P) reduces the incidence of recurrent preterm delivery in women with history of spontaneous preterm delivery.

Taking as a whole, the review of the data pointed out that the prophylactic use of progesterone results beneficial in reducing preterm delivery and low-weight at birth. Data also indicate, in a minor concluding way, that progesterone can improve the rates of neonatal morbidity and mortality<sup>30</sup>.

Intramuscular route-progesterone is associated with a reduction of premature delivery before the 37<sup>th</sup> week, and with a newborn infant inferior to 2500 gram-weight, observing a lesser degree of cervical shortening, confirming that the use of 17  $\alpha$ -hydroxyprogesterone (17  $\alpha$  OH P) was related with a reduction of premature delivery (OR: 0,15; IC 95%, 0,04-0,58)<sup>31,32</sup>.

Hassan and Romero, et al. stated in their work that the use of intramuscular 17-hydroxyprogesterone

caproate or vaginal micronized during 18<sup>th</sup> and 22<sup>th</sup> week up to the 36<sup>th</sup> week in patients with history of premature delivery or a cervix shorter than 15 mm reduces by 50% the risk for another preterm delivery<sup>33</sup>. It was demonstrated in 2011, that the finding of a cervical length between 10-20 mm at the beginnings of the second term, constitutes an indicator to administrate progesterone as well, and that its use not only could reduce the incidence of prematurity, but also its associated morbidity<sup>34</sup>.

## IX. THERAPEUTIC APPROACH<sup>35-40</sup>

To date, when progesterone is used to prevent preterm delivery, the following approach can be applied based on the available data:

1. For women having a previous spontaneous premature delivery: to administer 17 $\alpha$  OH P (250 mg) weekly, starting at 16<sup>th</sup> and 24<sup>th</sup> weeks.
2. For women having a short cervix (<25 mm): vaginal progesterone suppositories of 200mg can be administered in reasonable doses of 250mg weekly of 17 $\alpha$  OH P.
3. For women having a twin pregnancy: progesterone is not systematically indicated, even though its use can be effective in the context of a previous spontaneous premature delivery or a very short cervix: 250 mg of intramuscular 17 $\alpha$  OH P weekly or 200 mg vaginal suppositories.
4. For women having preterm labor arrest: the administration of progesterone could be considered (400 mg daily in vaginal suppositories or 250 mg of intramuscular 17 $\alpha$  OH P, twice a week), but the available data are so limited because of the lack of blind trails.

However, results have been satisfactory with the administration of progesterone in some of its presentations (intramuscular or vaginal) for many authors, and there are recent articles published from 2013, along with multicenter studies carried out in United States and Great Britain along with a study done in Spain with pregnant women having short cervix detected by cervicometry and history of preterm delivery. Cervical cerclage was performed to a group of 142 pregnant women, 59 of them were administered progesterone and to 42 a silicone device (pessary) was placed around the cervix, the conclusions of this study did not contribute to significantly statistical results<sup>40</sup>, showing that an only therapy or behavior will not solve the problem and that in occasions two therapies should be applied, as cervix cerclage and progesterone could be, even though researches must continue.

## X. CONCLUSION

Preterm delivery is a health problem even in the middle of 21<sup>st</sup> century due to the high levels of morbidity and mortality, which has a multifactorial etiology, but

almost a third of births before a gestational age of 37 complete weeks are consequences of an early modification of cervix, therefore prophylactic measures can help, an ultrasonography cervicometry must be performed to predict preterm delivery where the different features of cervix can be assessed, comprising: the length of cervix, existence of funneling or amniotic fluid with *sludge*, performing these assessments between 18<sup>th</sup> and 24<sup>th</sup> weeks of pregnancy. In the case a shortening of cervix is confirmed or the patients refer one or more previous preterm deliveries, then a progestin therapy by vaginal route or intramuscular 17-hydroxyprogesterone should be established, preferably up to the 36<sup>th</sup> week if necessary, as a result different therapeutic approaches in both aspects are explained, as well as in twin pregnancy and with limited results, in cases presenting arrested preterm deliveries. The greater part of works support the weekly injections of 17-hydroxyprogesterone, a supplementation that also reduces the frequency of recurrent preterm delivery, particularly in patients presenting high risks for premature births reducing the probabilities of numerous complications in newborn infants.

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# Fibroadenoma en Glándula Mamaria Supernumeraria Axilar: Presentación De Un Caso Fibroadenoma in Axillary supernumerary Breast: Presentation of a Case Investigación

By Pedro Manuel Bustamante Bohigas & Gloria Eugenia Camargo Villalba  
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*Resumen- Introducción:* El Fibroadenoma es el tumor benigno más común de la glándula mamaria femenina y está conformado por tejido fibroso y glandular, la mayoría de ellos se presentan en glándulas mamarias tópicas sin embargo un número muy escaso de ellos se desarrollan en glándulas mamarias de localización ectópicas que resultan por alteraciones del desarrollo a lo largo de las líneas mamarias embrionarias.

*Objetivo:* Presentar un caso clínico de fibroadenoma en glándula mamaria axilar ante la comunidad científica, teniendo en cuenta su poca frecuencia.

*Métodos:* Revisión de literatura, presentación de historia clínica completa con estudios de anatomía patológica, análisis de los resultados y conclusiones.

*Conclusiones:* Ante una masa de localización axilar es indispensable elaborar una historia clínica detallada, con estudios complementarios de imágenes diagnósticas y de anatomía patológica que permita ofrecer un tratamiento específico.

*Palabras Clave:* mama, neoplasias de la mama, fibroadenoma.

*GJMR-E Classification :* NLMC Code: WJ 190



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# Fibroadenoma en Glándula Mamaria Supernumeraria Axilar: Presentación De Un Caso Fibroadenoma in Axillary supernumerary Breast: Presentation of a Case Investigación

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**Resultados:** Confirmación mediante estudios de anatomía patológica de un fibroadenoma intracanalicular, en una glándula mamaria Axilar.

**Conclusiones:** Ante una masa de localización axilar es indispensable elaborar una historia clínica detallada, con estudios complementarios de imágenes diagnósticas y de anatomía patológica que permita ofrecer un tratamiento específico.

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**Introduction:** The Fibroadenoma is the most common benign tumor of the feminine mammary gland and is shaped by fibrous and glandular fabric, the majority of they they present in hackneyed mammary glands nevertheless a very scanty number of them develop in ectopic mammary glands of location that prove for alterations of the development along the mammary embryonic lines. I target: To present a clinical case of fibroadenoma in gland would suck axilar before the scientific community, bearing frequency in mind his small.

**Methods:** Review of literature, presentation of clinical history completes with studies of pathological anatomy, analysis of the results and conclusions.

**Results:** Confirmation by means of studies of pathological anatomy of a fibroadenoma intracanalicular, in a gland would suck Axilar.

**Conclusions:** Before a mass of location axilar is indispensable to elaborate a clinical detailed history, with complementary studies of diagnostic images and of pathological anatomy that allows to offer a specific treatment.

**Keywords:** breast, neoplasias of the breast, fibroadenoma.

## I. INTRODUCCION

El propósito del artículo es presentar y discutir un caso inusual de fibroadenoma intracanalicular localizado en una glándula mamaria ectópica axilar derecha.

Se trata de una paciente de 27 años de edad quien consulta por sensación de masa axilar derecha ligeramente dolorosa, se realiza biopsia excisional y el estudio de anatomía patológica informa glándula mamaria ectópica de localización axilar con fibroadenoma simple intracanalicular.

Las alteraciones del desarrollo mamario se presentan hasta en un 10% de la población (1,2), son más frecuentes en mujeres que en hombres (3), el tejido mamario aberrante (ectópico) se encuentra hasta en un 6% y se presenta en el trayecto de la línea mamaria embrionaria, siendo más común en tórax, axila y vulva (4), en el tejido mamario aberrante, se pueden desarrollar procesos patológicos tanto de carácter benigno como maligno (5),

El Fibroadenoma es un tumor benigno de la glándula mamaria compuesto por tejido glandular y conjuntivo; es más frecuentes en mujeres de 20 a 39 años de edad, sin embargo puede presentarse a cualquier edad. El uso de anticonceptivos orales antes de los 20 años está asociado con el riesgo de presentación de esta lesión. (6)

Algunos de estos tumores son demasiado pequeños situación que dificulta su palpación y se requiere la utilización de ayudas diagnósticas imagenológicas para su detección, otros por su tamaño se detectan clínicamente y se presentan como un nódulo, móvil, de consistencia elástica, bordes definidos y generalmente no dolorosos a la palpación, estas lesiones pueden ser únicas o múltiples, se denominan fibroadenomas simples no representan un

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factor de riesgo para el desarrollo de cáncer en la glándula mamaria; otros fibroadenomas denominados complejos poseen alteraciones apocrinas, calcificaciones y/o cambios de tipo de adenosis esclerosante, se considera y representan un factor de riesgo para el desarrollo de una neoplasia maligna.

## II. PRESENTACIÓN DEL CASO

Paciente de sexo femenino, mestiza de 27 años de edad, quien consulta a institución de salud de tercer nivel, al servicio de urgencia, en Tunja (Boyaca-Colombia) por presentar masa axilar derecha dolorosa sin otra sintomatología asociada. Antecedentes: Menarquía y Telarquia a los 13 años, G0P0A0, sin

antecedentes familiares de cáncer. Al examen físico presenta una masa subcutánea móvil en región axilar derecha de aproximadamente 4 cm. de diámetro, moderadamente dolorosa a la palpación. Resto de Examen físico negativo.

Se realiza biopsia excisional y el estudio anatómico patológico informa una masa blanquecina de consistencia elástica de 3x1.5x1 cm. sólida de superficie nodular homogénea (Figura 1), a nivel histológico se observa proliferación de estroma conjuntivo laxo que rodea y comprime los conductos mamarios histológicamente normales, características típicas de un Fibroadenoma simple intracanalicular. (Figuras 2,3). La paciente actualmente se encuentra asintomática.

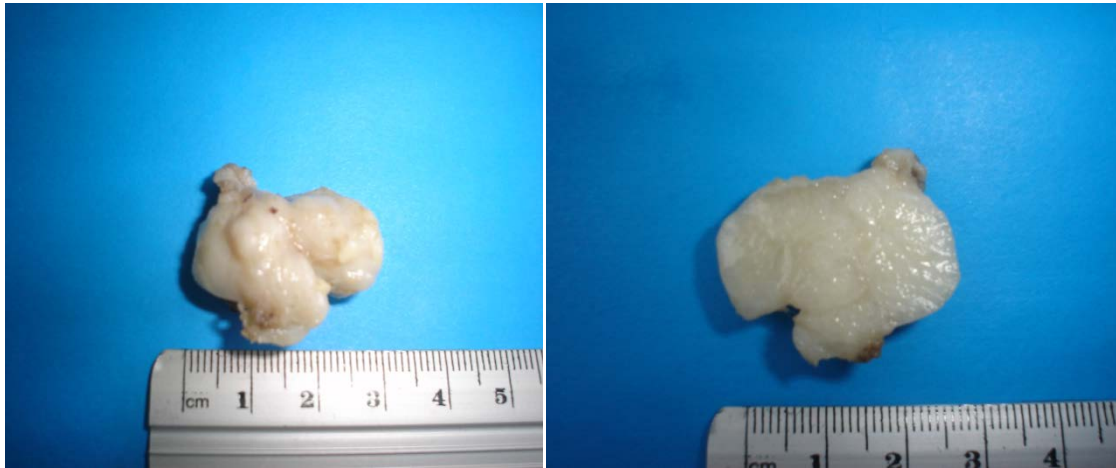


Figure 1 : Masa blanquecina de aspecto nodular y superficie de corte homogénea. Fuente: Los autores

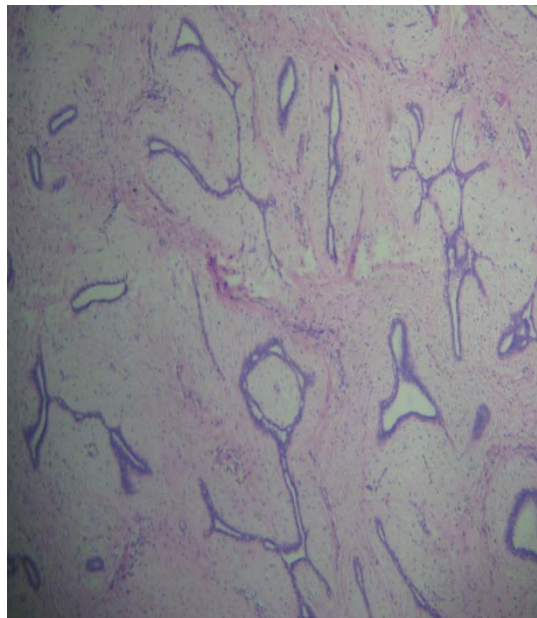
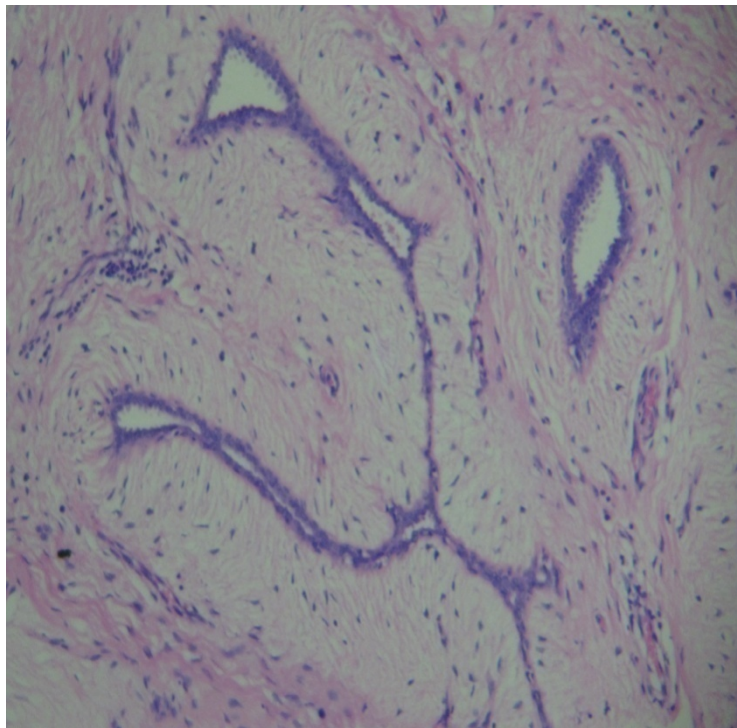


Figure 2 : Menor aumento se observa proliferación del estroma conjuntivo laxo comprimiendo los conductos mamarios fuente: los autores





*Figure 3:* Mayor aumento: se observa proliferación de estroma conjuntivo laxo y células ductales de características normales. Fuente. Los autores

### III. DISCUSIÓN

El Fibroadenoma es una causa común de masa en la glándula mamaria. Corresponde al 13 % de todas las masas sintomáticas palpables (7). Esta enfermedad se presenta con mayor frecuencia en la tercera década de la vida, como nódulo único o múltiple de consistencia elástica, siendo poco comunes los que sobrepasan dimensiones mayores de cuatro centímetros; no presenta recurrencias y desde el punto de vista patológico se clasifica en Fibroadenoma común, gigante, juvenil y tumor Phyllodes. De acuerdo a su estructura histológica, pueden ser simples o complejos, intracanaliculares o pericanaliculares, estas lesiones son infrecuentes en glándulas mamarias ectópicas (8,9,10,11). De acuerdo con los trabajos de Dupont y Page los fibroadenomas mamarios constituyen un riesgo a largo plazo para el desarrollo de cáncer de mama (12). En el presente caso de fibroadenoma simple de patrón intracanalicular en tejido mamario ectópico (axilar derecho) es difícil establecer y valorar las particularidades del desarrollo y progresión de la lesión debido a la ausencia de estudios clínicos y exámenes paraclínicos previos como son estudios de imágenes diagnósticas y de patología. El diagnóstico definitivo se estableció con el estudio histopatológico del espécimen obtenido por tumorectomía y no representa un difícil reto terapéutico dadas sus características de benignidad, no obstante; el presente caso ilustra ampliamente al médico tratante acerca de la necesidad de considerar ante hallazgos similares la

posibilidad de glándula mamaria aberrante en el trayecto de las líneas mamarias embrionarias como es el caso publicado por Aughstee A.A y, Almasad J K., en el cual se efectuaron estudios previos de imágenes como la mamografía y posteriormente estudios de biopsia por aspiración con aguja fina, previo a la extirpación de la masa. Es importante establecer un diagnóstico diferencial que contemple la posibilidad de patología mamaria tanto benigna como maligna (13,14,15,16,17) así como inflamaciones, neoplasias mesenquimales benignas como lipoma, neoplasias benignas de anexos cutáneos y gangleos linfáticos reactivos o metástasis (18,19,20,21).

Los autores declaran no tener conflictos de interés con respecto al presente artículo.

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## Comportamiento Del Cáncer Cervico Uterino Según Citología Orgánicas Anormales En Nuevitas Del 2006 Al 2010

By Caridad Santana Serrano , Mavel Chávez Roque,  
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*Introducción-* Los tumores genitales femeninos representan una quinta parte de la totalidad existente de dicha enfermedad. El más frecuente es el de cérvix, que se ubica actualmente como el segundo cáncer más común en la población femenina mundial. La incidencia por Cáncer Cervicouterino (CCU) se encuentra en franco aumento alcanzando el 25% en el año 2006 y su incidencia varía por todo lo ancho de la geografía.<sup>1-3</sup>

Se ha destacado que la incidencia del Cáncer Cervicouterino varía de unas naciones a otras. Se observan tasas muy bajas en Israel y EEUU. La tasa de mortalidad en los países en desarrollo es dos veces la tasa de los países desarrollados. Anualmente mueren 231.000 mujeres por esta causa.<sup>3,4</sup>

En América Latina y El Caribe sus tasas de incidencia son elevadas y fallecen más de trescientas mil mujeres por esta enfermedad; las mayores incidencias se observan en Perú, Brasil, Paraguay, Colombia y Costa Rica; y se reportan tasas inferiores en Puerto Rico y Cuba.<sup>3</sup>

*GJMR-E Classification : NLMC Code: WJ 190, WS 360, QZ 20.5*



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# Comportamiento Del Cáncer Cervico Uterino Según Citología Orgánicas Anormales En Nuevitas Del 2006 Al 2010

Caridad Santana Serrano <sup>α</sup>, Mavel Chávez Roque <sup>σ</sup>, Leida Nilda Viñas Sifontes <sup>ρ</sup>  
& Maigret Calderon Cruz <sup>ω</sup>

## I. INTRODUCCIÓN

Los tumores genitales femeninos representan una quinta parte de la totalidad existente de dicha enfermedad. El más frecuente es el de cérvix, que se ubica actualmente como el segundo cáncer más común en la población femenina mundial. La incidencia por Cáncer Cervicouterino (CCU) se encuentra en franco aumento alcanzando el 25% en el año 2006 y su incidencia varía por todo lo ancho de la geografía.<sup>1-3</sup>

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Un estudio nacional muestra que más de mil mujeres son notificadas en el Registro nacional de neoplasia con cáncer del cérvix. Las tasas más altas son reportadas en las provincias orientales, fundamentalmente en Camagüey, Holguín y Guantánamo; con edades que oscilan entre 35 y 55 años (alrededor del 60 %); con una media de 40 años. En Cienfuegos se reportaron 12,7 por ciento de mujeres atendidas en el programa que presentaron esta enfermedad. Según Mendoza, <sup>5</sup> esta oncopatía es la quinta causa de muerte por cáncer en la provincia de Camagüey.

Por la importancia que se le atribuye a la detección temprana de esta patología, en varios países fundamentalmente los desarrollados, se aplican Programas de Diagnóstico Precoz del Cáncer Cervicouterino. No dejan de esforzarse los países del

Tercer Mundo, entre ellos se encuentran, al decir de Schiavon,<sup>5</sup> que en México, desde 1974 se aplica el programa; y la operatividad del mismo fue reformulada de manera importante en el año 2000. El propio autor señala que entre el 20% y el 60% de estas muertes se podrían prevenir mediante el uso efectivo y temprano del citado programa. En Chile existe uno similar desde 1987.<sup>6</sup>

El Ministerio de Salud Pública de Cuba ha desarrollado un Programa Nacional para el Diagnóstico Precoz del Cáncer Cervicouterino desde 1968, con el objetivo de realizar un diagnóstico temprano de la oncopatía y así dedicarse a las ventajas curativas que ofrece esta localización del cáncer, que puede ser curada hasta de un 100% cuando el mismo se detecta de forma precoz.<sup>7</sup> Este programa, a través de todos estos años, ha sufrido modificaciones favorables, y se ha actualizado en la presente década.

Existe un elevado índice de mujeres con patologías de cuello en el municipio de Nuevitas, y entre ellas se observa la incidencia de morbimortalidad por CCU, en particular se aprecia una alta presencia de Papiloma Virus Humano en las citologías orgánicas positivas.

Sobre la base de lo planteado, fue motivo de la realización de la presente investigación con el objetivo de determinar el comportamiento del CCU a partir de resultados anormales de las citologías orgánicas en Nuevitas, desde el 2006 al 2010, además se quiso corroborar si existe relación de las pacientes con citologías orgánicas positiva y la presencia de Papiloma Virus Humano.

## II. DISEÑO METODOLÓGICO

Se realizó un estudio descriptivo transversal para determinar el comportamiento del CCU detectado mediante las citologías orgánicas anormales, en el Policlínico Universitario "Francisco Peña Peña" en el municipio de Nuevitas, desde enero del 2006 a diciembre de 2010.

De un universo de 218 mujeres con citologías orgánicas anormales en el Área de Salud de Nuevitas se tomó como muestra todas las pacientes.

Se realizó una revisión documental de las tarjetas de citologías orgánicas de las pacientes, y

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luego se aplicó el método empírico mediante la confección de una guía o encuesta (Anexo 1); la cual contenía las variables seleccionadas por los autores, entre ellas: edad, conductas sexuales irresponsables y antecedentes de infecciones de transmisión sexual, en particular del papiloma virus humano.

Se utilizó el método estadístico descriptivo, los datos se expresaron en frecuencia absoluta y porcentajes. La información recolectada según etapa fue procesada a través de medios automatizados con los

paquetes estadísticos en Microsoft Excel 2003 para Windows en el cual se realizaron base de datos y distribución de frecuencias. Los textos se procesaron con Microsoft Office Word, y las tablas y gráficos se realizaron en Excel.

Implicaciones éticas: se tuvo en cuenta la ética en todos los casos, cada encuesta llenada fue anónima, sin divulgar datos en el orden particular de ninguna de las pacientes estudiadas.

### III. RESULTADOS

**Tabla 1 :** Distribución de pacientes con resultados anormales en las citologías orgánicas realizadas según grupo de edades en el Policlínico Comunitario Docente "Francisco Peña Peña" de Nuevitas desde el 2006 al 2010

Edades (años)	No	%
- 25 años	19	8,72
De 25 a 34	57	26,15
De 35 a 44	88	40,37
De 45 a 54	42	19,27
De 55 a 64	10	4,59
+64 años	2	0,92
<b>Total</b>	<b>218</b>	<b>100,00</b>

*Fuente :* Tarjeta de citología orgánica.

Entre los resultados de las citologías orgánicas anormales según grupos de edades, en el Área de Salud de Nuevitas, desde el 2006 al 2010, se observó que el mayor número corresponde a mujeres entre 35 y

44 años, para un 40,37 %. Es importante destacar que 19 mujeres menores de 25 años presentaron citologías orgánicas positivas para un 8.72%. (Tabla 1)

**Tabla 2 :** Factores de riesgos del cáncer cérvicouterino según conducta sexual

Conducta sexual	No	%
Sexo desprotegido (condón)	218	100,00
Primeras relaciones sexuales antes de los 19 años	177	81,19
15 y menos	54	24,77
De 16 a 17	73	33,49
Entre 18 a 19	51	23,39
Cambio Frecuente de Pareja	125	57,34

*Fuente :* Tarjeta de citología orgánica. n=341

En la Tabla #. 2 se observó que la conducta sexual de las pacientes en un 100% eran desprotegidas. La mayoría de las pacientes tuvieron las

primeras relaciones sexuales antes de los 19 años y el 57.34 % cambiaban frecuentemente de parejas.

**Tabla 3:** Incidencia del cáncer cérvicouterino según Infecciones de Transmisión Sexual

Infecciones de Transmisión Sexual	No	%
PVH/diagnóstico cito-histológico	164	75,23
Chlamydias	150	68,81
Herpes virus	46	21,10
Trichomonas	31	14,22
<b>.n=341</b>		
Infecciones de Transmisión Sexual	No	%
PVH/diagnóstico cito-histológico	164	75,23
Chlamydias	150	68,81
Herpes virus	46	21,10
Trichomonas	31	14,22
<b>.n=341</b>		

*Fuente:* Tarjeta de citología orgánica.

Los antecedentes de enfermedades de transmisión sexual se ven reflejados en la tabla 3 (gráfico 1), donde en el 75,23% de las estudiadas se detectó la presencia de PVH a través del diagnóstico cito-histológico, asociadas a otras infecciones vaginales.

#### IV. DISCUSIÓN

A la mayoría de las pacientes se les diagnosticó la presencia del CCU mediante la citología orgánica, por lo que se demuestra que esta sigue siendo el método diagnóstico de mayor valor para detectar Neoplasia Intraepitelial Cervical (NIC) y Carcinoma en estadio precoz en grandes masas de población, por la sencillez en su realización y su alta eficacia. Lo realmente eficaz ante el diagnóstico del Cáncer de cérvix es establecerlo en una etapa precoz lo que se confirma en varios estudios.<sup>7,8</sup> Martínez<sup>9</sup> plantea que en la actualidad la neoplasia cervicouterina es una de las enfermedades más frecuentes en la mujer, lo importante es establecer un diagnóstico temprano y oportuno para disminuir la morbimortalidad por dicha entidad.

Las citologías orgánicas anormales en Nuevitas, se observó que el mayor número corresponde a mujeres entre 35 y 44 años seguido del grupo entre 25 y 34 años. López<sup>10</sup> encontró que el mayor número de mujeres con citologías positivas tenían entre 45 – 54 años de edad, con un 57.14 por ciento.

Por otro lado, en presente estudio se observó un número significativo de mujeres menores de 25 años con citologías anormales, las que coinciden con el número de pacientes con conductas sexuales inadecuadas,; el estudio de Vázquez<sup>11</sup> corrobora esta

idea, destacando que la aparición del cáncer del cuello de útero también se observa en edad precoz, a pesar de ser considerado como un cáncer de la perimenopausia, observando además una alta prevalencia en las pacientes que se encontraban en edad reproductiva; de ellas el 43,6 % eran menores de 40 años, incluyendo 3 (0,9 %) con menos de 20 años. Martínez et al<sup>12</sup> encontró que la quinta parte de citologías orgánicas positivas correspondía a menores de 25 años. Estos datos relacionados con citologías orgánicas patológicas antes de los 25 años, en mujeres con algún factor de riesgo asociado, hacen meditar a los médicos y enfermeros de la familia sobre la actuación en las jóvenes de su comunidad con factores de riesgos que deben ser incluidas en el programa, pues se puede confirmar que la citología orgánica del cérvix es el método ideal para realizar un diagnóstico temprano y oportuno de este tipo de cáncer.

Las citologías orgánicas positivas se aprecian, con mayor frecuencia, en mujeres que comienzan sus relaciones sexuales antes de los 19 años, influyendo además otras conductas sexuales irresponsables como la promiscuidad y las relaciones sexuales desprotegidas. Estudios reflejan que en cuanto a la edad de inicio de las primeras relaciones sexuales se precisó que en el grupo de estudio el mayor por ciento lo alcanzó las que comenzaron antes de los 16 años.<sup>13</sup>

Los estudios epidemiológicos de las lesiones del cuello uterino relacionados con los factores de riesgos del CCU, han demostrado una fuerte asociación entre la práctica sexual y la aparición de tumores malignos. Se indica que las mujeres con múltiples patrones sexuales, embarazos e interrupciones a temprana edad e historias de infecciones, aumentan el

riesgo de padecer la enfermedad,<sup>14</sup> elementos de valor representativo en el presente estudio. Diversas investigaciones muestran el comportamiento de estos factores de riesgos predisponentes para padecer de esta oncopatía.

Martínez C<sup>9</sup>, señala la asociación existente entre las relaciones sexuales precoces y el Cáncer cervical, afirmando que mientras más jóvenes practicaban estas relaciones, más severa se comportó la enfermedad, aspecto que confirma, Sarduy,<sup>15</sup> quien también encontró en su estudio que entre los factores de riesgos se observaron las primeras relaciones sexuales antes de los 18 años, lo que reafirman además Vázquez<sup>11</sup> y Aguilera.<sup>16</sup> Martínez Y.<sup>17</sup> encontró que 70 adolescentes procedentes de las consultas Infanto-juvenil y Patología de Cuello, con los siguientes resultados: con sexarquía antes de los 16 años un 88,6 %; no usaban métodos anticonceptivos de barrera el 68,6 %, de ellas 50 tenían colposcopia positivas y 38 biopsias con lesiones intraepiteliales cervicales. De igual forma Herrera<sup>18</sup> expresó que el factor de riesgo más relevante encontrado fue el inicio precoz de las relaciones sexuales, donde 13 pacientes iniciaron su vida sexual antes de los 20 años para un 56.5 por ciento. Tamayo<sup>18</sup> comprobó en su estudio que el inicio precoz de las relaciones sexuales está asociado con las lesiones de alto grado de cuello uterino, el 56.5 por ciento de mujeres con CCU iniciaron sus relaciones sexuales precozmente. López,<sup>10</sup> encontró resultados similares donde el 50 por ciento tuvieron su relación sexual entre 15 – 19 años.

El factor de riesgo relacionado con el cambio frecuente de pareja se observó en más de la mitad de las pacientes con citologías patológicas, lo que se comprueba por otros estudios.<sup>5,19,20</sup> Rosell et al,<sup>21</sup> observaron predominio en el 96,78 por ciento en mujeres que tuvieron tres o más compañeros sexuales; también fueron factores de riesgo las primeras relaciones sexuales en la adolescencia.

Otro factor importante observado en estas pacientes fue el sexo desprotegido, aspecto encontrado por otros autores.<sup>6,7</sup>

El aumento en los últimos años del Cáncer Cervical y sus lesiones precursoras, ha conllevado a la realización de varios estudios de factores de riesgo y dentro de ellos señalan la fuerte asociación de este cáncer con el Virus del Papiloma Humano (HPV), encontrando en más de las dos terceras partes de las pacientes estudiadas la presencia de este virus detectado a través del diagnóstico cito-histológico, asociadas a otras infecciones vaginales, muestra de las conductas sexuales irresponsables desde edades tempranas, resultados similares expresan otros estudios.<sup>5,7,22</sup>

El comportamiento de algunos factores de riesgo que contribuyen a la aparición del cáncer cérvicouterino, en estudios realizados por autores,

reportan que un 47,27% tenían el antecedente de infección vaginal por PVH.<sup>23,24</sup>

Varios autores señalan que, la neoplasia cervicouterino es considerada como una infección de transmisión sexual, más bien se trata del resultado final de la acción de varios factores donde las infecciones de transmisión sexual desempeñan un papel muy especial.<sup>3,9</sup> La OMS considera que las ITS constituyen, a escala mundial, la segunda causa de enfermedad más importante en mujeres jóvenes de países en desarrollo.<sup>25</sup>

El HPV es el principal agente etiológico infeccioso asociado con la patogénesis del cáncer de cuello uterino<sup>26</sup>. Se plantea que el conocimiento de la virología y las manifestaciones clínicas de este virus, constituyen el eslabón fundamental en el proceso neoplásico.<sup>11</sup>

Se ha logrado identificar más de 100 serotipos de PVH; de ellos, 30 tipos asociados al Cáncer Cérvicouterino, los que se clasifican en virus de alto grado oncogénico: 16, 18, 31, 45, 56, que son hallados en lesiones de alto grado (NIC II, NIC III y carcinoma in situ) y cáncer invasivo que se asocian en 95% de los casos<sup>8</sup> Los condilomas acuminados son producidos por virus de bajo riesgo oncogénico en el 90% de los casos, pero son un importante marcador para la infección con virus de alto riesgo oncogénico.<sup>27</sup>

La infección por VPH en el aparato genital, sobre todo algunos subtipos llamados oncogénicos, juegan un papel relevante en la aparición de las lesiones intraepiteliales y su posible evolución al cáncer invasor en esas localizaciones.<sup>14</sup>

Entre los factores de riesgo o antecedentes de ITS se reportaron en el 91,3 por ciento, predominando PVH en el 60,8 por ciento unidos a otros.<sup>17,28</sup>

Se realizó una investigación en Brasil sobre la infección por HPV en 99 hombres que eran parejas sexuales de las mujeres que tenían Neoplasia Intraepitelial Cervical (NIC). A estos hombres se les realizó un examen físico y peneoscopia, detectando que el 54,5 % presentaban el HPV y un 28 % presentaron lesiones clínicas evidentes.<sup>29</sup>

Las ITS incluyen una serie de enfermedades de naturaleza infecciosa de gran interés epidemiológico y señalan que la *Neisseria gonorrhoeae* se dispone en parejas intracelulares, y que habitualmente afecta los epitelios cilíndricos, pues los epitelios estratificados de la vulva y vagina son resistentes a su invasión.<sup>3</sup> Otros estudios encontraron trichomoniasis en un 55 % de las pacientes y el HPV que resultaron ser los que más se asociaron con esta neoplasia.<sup>11,30</sup>

De los resultados obtenidos de la citologías orgánica de cuello uterino fueron positivos de PVH el 57 % ,4 % arrojaron resultados de NIC I, y 1% NIC II.<sup>25</sup>

El Papiloma Virus Humano (PVH) ha sido implicado como el agente causal del condiloma acuminado y de carcinomas anogenitales. El artículo

plantea el importante papel que juega el tamizaje cervical oportuno y periódico en la prevención del cáncer<sup>31</sup>

Casi la mitad de los casos presentaron colposcopia anormal; en la citología orgánica, más de la mitad de los casos presentaron positividad al PVH, se diagnosticaron un 4 por ciento de NIC I y un 1 por ciento de NIC II.<sup>31</sup>

En sentido general, se observó una gran relación entre las citologías orgánicas anormales y las acciones y consecuencias relacionadas con las conductas sexuales irresponsables como factores de riesgos que pueden influir en el desarrollo del CCU en la población femenina; destacar que las mujeres más expuestas a padecer la enfermedad son las que presentan varios factores de riesgos asociados, por lo que es imprescindible la caracterización adecuada de cada mujer en el consultorio para poder realizar intervenciones de salud encaminadas a cambiar estilos de vida y así disminuir los riesgos de padecer esta temible oncopatía.

## V. CONCLUSIONES

El mayor grupo de edad con citologías orgánicas positivas fue el de 25 a 44 años, siendo significativo la aparición de lesiones premalignas en menores de 25 años.

Relacionado con la conducta sexual, la mayoría de las pacientes tuvieron su primera relación sexual antes de los 19 años y la promiscuidad primó entre las estudiadas.

La ITS por PVH se en la mayoría de los casos.

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## The Mythical G-Spot: Past, Present and Future

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**Summary-** The so-called point Gräfenberg popularly known as "G-spot" corresponds to a vaginal area 1-2 cm wide, behind the pubis in intimate relationship with the anterior vaginal wall and around the urethra (complex clitoral) that when the woman is aroused becomes more sensitive than the rest of the vagina. Some women report that it is an erogenous area which, once stimulated, can lead to strong sexual arousal, intense orgasms and female ejaculation. Although the G-spot has been studied since the 40s, disagreement persists regarding the translation, localization and its existence as a distinct structure.

**Objective:** Understand the operation and establish the anatomical points where the point G from embryology to adulthood.

**Methodology:** A literature search in the electronic databases PubMed, Ovid, Elsevier, Interscience, EBSCO, Scopus, SciELO was performed.

**Results:** descriptive articles and observational studies were reviewed which showed a significant number of patients.

**Conclusion:** Sexual pleasure is a right we all have, and women must find a way to feel or experience orgasm as a possible experience of their sexuality, which necessitates effective stimulation.

**Keywords:** *G Spot; vaginal anatomy; clitoris; skene's glands.*

**GJMR-E Classification :** *NLMC Code: WP 250*



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# The Mythical G-Spot: Past, Present and Future

Dr. Franklin J. Espitia De La Hoz <sup>α</sup> & Dra. Lilian Orozco Santiago <sup>ο</sup>

**Summary-** The so-called point Gräfenberg popularly known as "G-spot" corresponds to a vaginal area 1-2 cm wide, behind the pubis in intimate relationship with the anterior vaginal wall and around the urethra (complex clitoral) that when the woman is aroused becomes more sensitive than the rest of the vagina. Some women report that it is an erogenous area which, once stimulated, can lead to strong sexual arousal, intense orgasms and female ejaculation. Although the G-spot has been studied since the 40s, disagreement persists regarding the translation, localization and its existence as a distinct structure.

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## 1. INTRODUCTION

In our opinion from the anatomical point of view, the "G-Spot" does not exist, as there is a separate anatomical unit, but neither can deny from the embryological point of view. In my experience I agree and acknowledge that many women who defend and swear they have it, unfortunately, science has not been able to locate it.

There are few studies that different scientists have used in finding the controversial "G-Spot": (Biopsies, surveys, scans, scans, ultrasounds, etc.) to locate the very controversial "G-spot".

It is called "G-spot" to a vaginal area 1-2 cm wide, located behind the pubic bone in the front of the vaginal wall and around the urethra about 3-5 cm from the outside of the vagina between the pubic bone and the cervix<sup>1</sup>, which is energized when the woman becomes more sensitive than the rest of the vagina. This

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<sup>1</sup> Burri AV, Cherkas L, Spector TD. Genetic and environmental influences on self-reported G-spots in women: a twin study. *J Sex Med* 2010; 7: 1842-1852.

region is named after the German gynecologist Ernst Gräfenberg Dr., which based on the observations of women during orgasm, in 1953 published an important article entitled "The role of urethra in female orgasm/ The role of the urethra in female orgasm": there described and suggested the existence of an erotic area 1-2 inches inside the vagina orgasms induced by direct mechanical stimulation<sup>2</sup>. However, it was until 1980, when the Ladas, Whipple and Perry doctors- which he guided by the findings reported in this article, which rediscovered the vaginal area and chose to name it as an area "G-spot"<sup>3,4</sup> Figure 1.

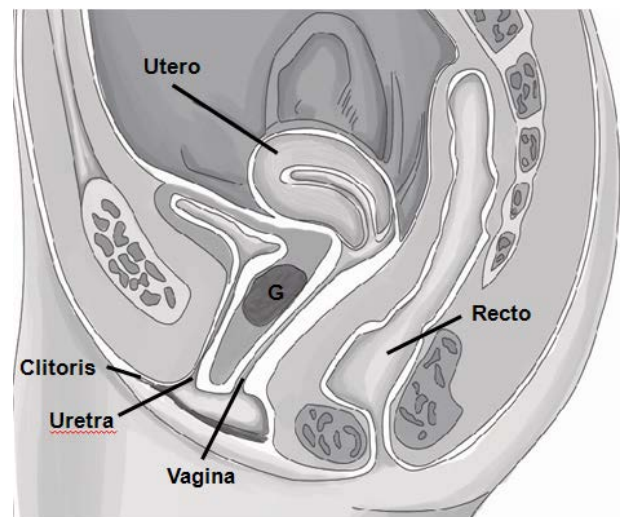


Figure 1 : The area or "G-Spot"

The anatomical proximity of the urethra and the clitoris to the anterior vaginal wall, suggesting an association between these structures and sexual function, and wherein the presence of tissue pseudocavernoso (vestibular bulbs of the clitoris) in the anterior vaginal mucosa a frequent finding (86%)<sup>5</sup>, I think more scientific interest in the clitoral complex.

Biopsies were performed vaginal tissue, but the results have not shown any particular structure, but some have emphasized and shown more nerve endings

<sup>2</sup> Gräfenberg R. The role of urethra in female orgasm. *Int J Sexol* 1950; 3: 146.

<sup>3</sup> O. Buisson, "Le point G ou l'absence de m'edecinesexuellef'em-inine," *Gyn'ecologieObst'etrique&Fertilit'e*, vol. 38, no. 12, pp. 781-784, 2010.

<sup>4</sup> Whipple B. Ernst Gräfenberg: From Berlin to New York. *Scandinavin Journal 5th Congress of the European Federation of Sexology* 2000; 3: 43-49.

<sup>5</sup> G. L. Gravina, F. Brandetti, P. Martini et al., "Measurement of the thickness of the urethrovaginal space in women with or without vaginal orgasm," *Journal of SexualMedicine*, vol. 5, no. 3, pp. 610-618, 2008.

exist at certain points in the other of the vaginal wall. Other ultrasound studies reported evidence that women who experience vaginal orgasms have thicker than those who do not have<sup>6</sup>, which leads me to speculate that there may be a functional correlation between the thickness of urethrovaginal space or "dot- space urethrovaginal G" and the ability to experience vaginal orgasm, and thus explain the importance, - to achieve orgasms -the region that would correspond to the "G-spot". In other studies involving the use of MRIs, the stimulation of the clitoris, the vagina and cervix lit different areas of the brain, leading to the conclusion that each part or structure of these generates a different reaction in the body. Which suggests that the "G-Spot" can be a whole area of the anterior vaginal wall, rather than a point in itself. What gives the scientific basis to suggest that the whole of: anterior vaginal wall, clitoris and urethra form a team that could be called clitoral complex<sup>7</sup>, complex to participate and be responsible for generating all the fun, and that simply stimulate anywhere in this area would result in infinity female pleasure, because it would be the location of female sexual activity, analogous to the penis in men, ie the correct anatomical term should be " invaginated female penis". Figure 2.

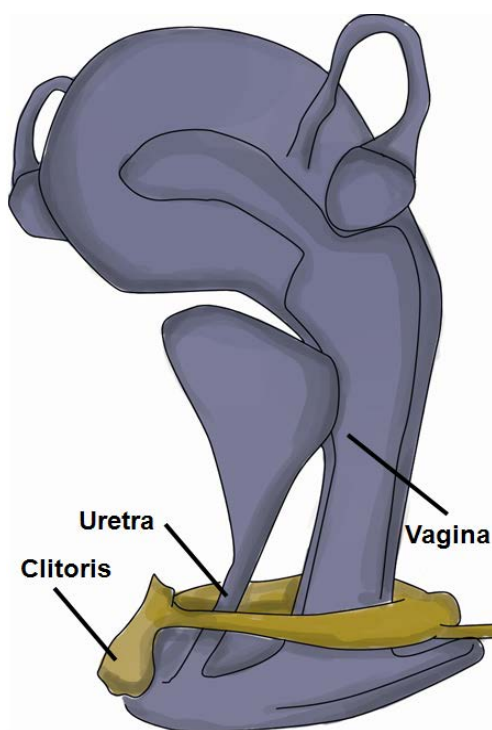


Figure 2 : Clitoral complex

<sup>6</sup> G. L. Gravina, F. Brandetti, P. Martini et al., "Measurement of the thickness of the urethrovaginal space in women with or without vaginal orgasm," *Journal of Sexual Medicine*, vol. 5, no. 3, pp. 610–618, 2008.

<sup>7</sup> V. Puppo, "The definition of "have sex" must be unique. Re: Mehta CM, et al: "Sex isn't something you do with someone you don't care about": young women's definitions of sex. *Journal of Pediatric and Adolescent Gynecology* 2011; 24:266– 71," *Journal of Pediatric and Adolescent Gynecology*.

Publications are many, for or against, but the truth is there is no anatomical ultrasound images or pictures of "G-Spot" and the female prostate lacks an anatomical structure that can cause an orgasm<sup>8,9</sup>. However, vaginal penetration causes close contact between the inner clitoris and the anterior wall of the vagina, which could explain this phenomenon.

It is through this review I want to make my opinion of why some women might have and others do not much discussed area or "G-spot", without being so blunt and absolutist in emphasis that does not exist, as if it was recorded some articles that there is no "G-spot", but if I clear that the "G-spot" does not exist as the magic button<sup>10</sup>, which many believe, the direct contact generates more pleasure, and emphasized that from the point of Embryologically has everything to be an area of the vaginal wall more nervous input and therefore more sensitive than the rest of the vagina, and it is obvious that the anterior wall of the vagina is an active organ that transmits during intercourse, the mechanical effect of the thrust of the penis into the vagina to the clitoris, through continuum and stretch the ligaments that are inserted around its base and the vestibular bulbs, which would theoretically the basis science of its existence.

## II. EMBRYOLOGY FEMALE GENITAL APPARATUS

The external genitalia are generated at the caudal end of the embryo by successive changes in the cloaca, which is divided into the urogenital sinus anteriorly and the anorectal canal behind: to the 5th and 6th week the caudal end of the embryo is blocked by the cloacal membrane, and in the 7th week on your front end the genital tubercle, and each side of the anteroposterior urogenital folds, and out of these, or labioscrotal genital swelling.<sup>11</sup>

In the absence of production of AMH, to the 8th, 9th, 10th and 11th week paramesonephric ducts or Müller (stimulated by maternal estrogens and placental) reach the pelvis of the embryo, where they cross in front of the mesonephric ducts or Wolf toward and juxtaposed<sup>12,13</sup>, each other, without merging further, and

<sup>8</sup> V. Puppo, "Embryology and anatomy of the vulva: the female orgasm and women's sexual health," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 154, no. 1, pp. 3–8, 2011.

<sup>9</sup> T. M. Hines, "The G-spot: a modern gynecologic myth," *American Journal of Obstetrics and Gynecology*, vol. 185, no. 2, pp. 359–362, 2001.

<sup>10</sup> V. Puppo, "The G-spot does not exist. Response by V. Puppo to the article "O. Buisson: the Gspot and lack of female sexual medicine. *Gynécologie Obstétrique & Fertilité* 2010; 38:781-84," *Gynécologie Obstétrique & Fertilité*, vol. 39, pp. 266–267, 2011.

<sup>11</sup> Taure M. "Anatomía del desarrollo" 4ta. Edición. Ed. Científico Médica. Barcelona 1965. Pág.539-577.

<sup>12</sup> Sadler TW. Aparato urogenital. En: Langman (Langman's Medical Embryology) Embriología médica con orientación clínica. 9ª edición. Buenos Aires: Editorial Médica Panamericana; 2005.



as is the utero- vaginal canal, which derive from the tube, uterus and upper vagina. The utero- vaginal canal begins to surround fused muscle tissue, which differs from the surrounding mesenchyme, this muscle tissue grows from the bottom up, uterus, vaginal encompassing the vertical portion of the duct to form the body of the uterus, and finally the background.<sup>14</sup> Figure 3.

The lower portion of the blind müllerian bind urogenital sinus Müller tuber , and urogenital sinus wall contact tuber Müller, grows towards the forming senovaginales vaginal bulb constituting sheet, which is and lengthens the distance between the uterus and the urogenital sinus, and the same tissue proliferates mesonephricuterovaginal lower end of duct , increasing the length of the vagina. In the 11th week the vagina is channeled and flows just behind the urethra. At the caudal end of the uterus and vagina in the upper portion, emit about cervical extension by way of "wings" that surround it and form the vaginal sac or vaginal vault. The lower end is closed by the hymen, which separates the lobby; ahead, the vagina<sup>15</sup>, the urethra is removed, and behind the rectum, mesodermal septa. Thus, the upper portion of the vagina is Paramesonephricus origin, and lower, of the urogenital sinus<sup>16</sup>.

The pelvic mesenchyme lying in front of the rectum into the cloacal membrane, separating it into an anterior or urogenital portion and a posterior or anal. The urogenital diaphragm closes below the urogenital groove between the urogenital folds (membranous bladder and urethra ) and the anal membrane closes the year, and the end of urogenital septum form the perineal body. In the 8th week the urogenital sinus communicates with the outside, and outputs the anus outside the rectum. In the 9th week the genital tubercle becomes the phallic part constituting the clitoris. In the 10th week the urethra and vagina open into the urogenital sinus which continues to lobby on its lower portion. The lobby is framed laterally by the labia minora and labioscrotal swellings become the labia majora<sup>17</sup>.

In short, the formation of the external genitalia originates from the same structures for both sexes: the urogenital sinus form, in women, the lower two- thirds of the vagina and urethra, the elongation of genital tubercle formed in women, the clitoris and the urethral folds do

not fuse, forming the labia minora, genital prominences, in women, the labia<sup>18</sup>.

The epithelium of the female urethra is of endodermal origin, while the connective tissue that surrounds muscle derived from the splanchnic mesoderm sheet, and towards the end of the first quarter, the epithelium of the prostatic urethra begins to proliferate and emerge several outgrowths that are introduced into the surrounding mesenchyme, and the cranial portion gives rise to the urethral and paraurethral (rudimentary homologues of the prostate) glands, the largest being the Skene's glands, which empty into the distal third of the urethra or introitus<sup>19,20</sup>.

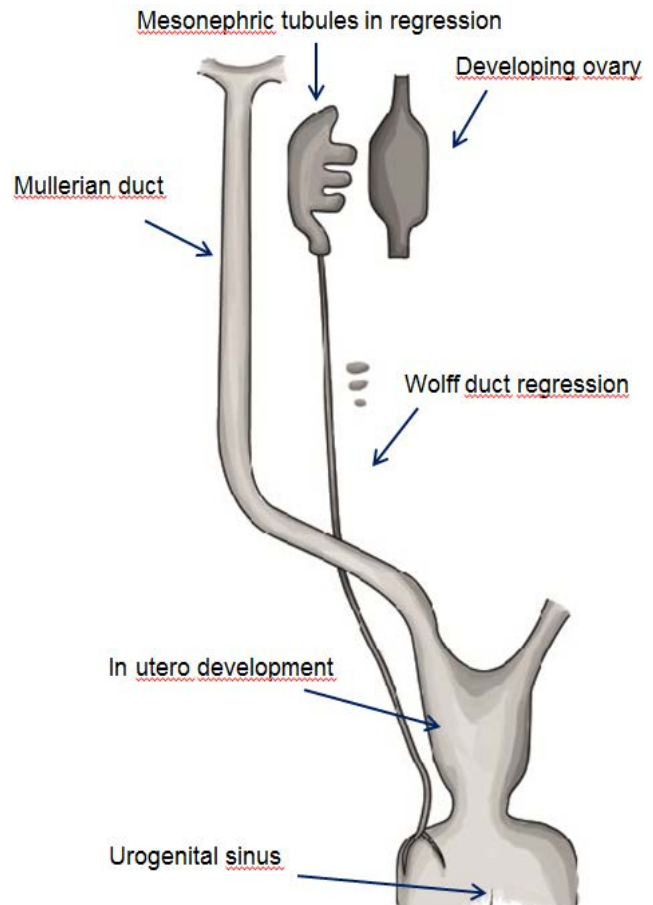


Figure 3 : Development of Mullerian ducts

### III. HISTOLOGY AND ANATOMY OF FEMALE GENITAL APPARATUS

#### a) Mount of Venus

Fat pad is a triangular shaped eminence in front of the pubic bones, resting on the anterior aspect of the

<sup>13</sup> Moore Persaud. "Embriología Básica" 5ta. Edición. McGraw-Hill. S: A. Interamericana. 2000. Pág. 334-353.

<sup>14</sup> Sadler TW. Embriología Médica (Langman). 7ma Edición. Editorial Panamericana 1996. Pag. 255-291.

<sup>15</sup> Solere M, Haegel P. "Embriologie" (Travaux Practiques. Enseignement Dirige) Tomo II. Masson e Cie Editeurs Paris 1967. Pag 75-104.

<sup>16</sup> Genis Gálvez JM. "Biología del desarrollo" Ed. Espax. Barcelona 1970. pág. 275-285.

<sup>17</sup> Bargmann W. "Histología y Anatomía microscópica Humanas" traducción española de la 5ta. Edición alemana por el Dr. Julio G. Sánchez Lucas - Editorial Labor Barcelona Bs. As 1964. Pág. 618-619.

<sup>18</sup> Pérez J, et al. Presentación de un casode hermafroditismo verdadero, con ovotestes descendidos a los pliegues labioscrotales. Urología Colombiana. 2006; 15:111-4.

<sup>19</sup> Sharif-Aghdas F, Ghaderian N. Female paraurethral cysts: Experience of 25 cases. BJU International 2003; 93:353-6.

<sup>20</sup> Pineaud, H; La croissance des Lois. Laboratoire D'Anatomie de la Faculté de Medicine de Paris. Paris 1965.



pubic symphysis, and is it covered by hair to its junction with the abdominal wall<sup>21</sup>.

#### b) Vulva

The set of external genital structures, and defined as localized in the anterior perineal triangle, bounded by the above mons, perineum later the inguinal folds laterally and medially hymenal ring area<sup>22</sup>. It is covered except the lobby area, stratified squamous epithelium and keratinized<sup>23</sup>.

The whole vulva includes the mons pubis, labia majora, minors, the inter-labial groove, the clitoris, the clitoral hood or prepuce, lobby or vaginal introitus, urethral meatus, the greater vestibular glands (Bartholin) in the posterior third of the lobby and lower (Skene) on either side of the urethral meatus<sup>24</sup>. Figure 4.

The blood supply comes from internal and external pudendal arteries. The anterior and superior regions are innervated by the ilioinguinal and genitofemoral (lumbar plexus) nerve and the rest by the pudendal nerve<sup>25</sup>.

#### c) Labia

Fibroadiposos are a couple of folds of skin that extend from the mons pubis down and backward to join in the line ahead of the year at the level of the rear fork, they are covered with keratinized stratified squamous epithelium. Include terminal extension of the round ligament. The skin is covered with sparse hair sideways and are rich in sebaceous glands, apocrine and eccrine and contain abundant adipose tissue and muscle liso<sup>26,27</sup>.

#### d) Labia minora or nymphs

Two mucosal folds that lie between the labia majora, with merging from behind, and are separated into two folds at the approach to the clitoris ahead. They are covered by squamous epithelium nonkeratinized except for a thin layer cornea at its side edges, beneath the epithelium richly vascularized and neat elastic fibers

in connective tissue is found, and in the medial portions consist of erectile spongy tissue traversed by beams collagen, associated with a complex network of elastic fibers, not containing hair follicles and sebaceous glands present few. The latest folds join to form the prepuce or clitoral hood. Subsequent folds form the frenulum of the clitoris. They are covered by hairless skin, overlying fibroelasticstroma rich in nervous and vascular elements. The area is in the rear parts of the labia minora is the vestibule of the vagina<sup>28, 29</sup>

#### e) Vagina

The vagina is a tubular structure, collapsed inside, extending from the lobby to the vulvar cervix measurement with 9 cm + / - 3, located posterior to the urethra and bladder and above the rectum, the wall anterior and posterior are brought into direct contact with each other, except in the 1/3 upper surrounding the cervix, and uterus with respect to an angle of 90°<sup>30,31</sup>.

The blood supply is the supply the vaginal artery and branches of the uterine artery, middle rectal and internal pudendal. The veins around the vagina forming uterine, rectal and pudendal veins that drain to the internal iliac vein<sup>32</sup>.

The innervation is supplied by the uterovaginal plexus (inferior hypogastric plexus) in virtually its entire course, but mainly in the upper middle portion and the lower portion measured by the pudendal nerve (sacral plexus)<sup>33</sup>, which also distributes motor and sensory branches to the region perineal and external genitalia. Innervates the external sphincter muscles of the anus and urethra, and ischiocavernosusbulboesponjoso and part of the levatorani, in addition to the skin in this region, as well as the labia and clitoris<sup>34</sup>.

The vaginal wall is made of three layers: mucous, muscular and adventitia<sup>35</sup>. The mucosa has a rough manner and form small folds of 2 to 5 mm thick according to the hormonal stimulation time (transverse folds) and is lined by stratified squamous non-keratinized epithelium, enriched Glycogen and receivers intranuclear for sex steroids<sup>36</sup>. Beneath the epithelium is

<sup>21</sup> MenendezLopez, V., GalanLlopis, J.A., Elia Lopez, M. et al. Sobre la necesidad del rasurado de la región púbica en los pacientes que van a ser sometidos a cirugía urológica endoscópica. *Actas Urol Esp.* [online]. 2004, vol. 28, no. 10 [citado 2013-11-24], pp. 761-765.

<sup>22</sup> Haefner H. Vulvar Anatomy. En: Black M, Ambros-Rudolph C, Edwards L, Lynch P, editores. *Obstetric and Gynecologic Dermatology*. Third ed. London: Mosby Elsevier; 2008. p. 124--31.

<sup>23</sup> Sternberg SS. *Histology for Pathologist*. Second ed. Philadelphia: Lippincot-Raven Publishers; 1997.

<sup>24</sup> Guerra Tapia A, Carrillo Gijón R, Rodríguez Peralto JL. Vulva normal. En: Guerra Tapia A, editor. *Manual y atlas de las enfermedades de la vulva*. Barcelona: Glosa; 2006. p. 13--5.

<sup>25</sup> Margesson LJ. Vulvar disease pearls. *DermatolClin*. 2006; 24: 145-55.

<sup>26</sup> De Ugarte CM, Bast JD. Embryology of the urogenital system & congenital anomalies of the female genital tract. En: DeCherney A, Murphy Goodwin T, Nathan L, Laufer N, editores. *Current diagnosis & treatment obstetrics & gynecology*. 10ª edición. Nueva York, McGraw-Hill. Med Pub Div.; 2007. p.64-94.

<sup>27</sup> Schroeder B. Vulvar disorders in adolescents. *ObstGynecolClinNorth Am*. 2000; 27:35-48.

<sup>28</sup> Capraro VJ. Congenitalanomalies. *ClinObstetGynecol*. 1971; 14:988.

<sup>29</sup> Fisher GO. Vulvar diseases in prepubertal girls. *Australas J. Dermatol*. 2001; 42 (41): 225-34.

<sup>30</sup> Kurgan Robert J, Norris Henry J. *Tumors of the cervix, vagina, and vulva*. Washington: AFIP. 2004. p. 200--202.

<sup>31</sup> Laterjet - Ruiz Liard. *Anatomía Humana*. Buenos Aires: Editorial Médica Panamericana; 1983.

<sup>32</sup> Platzer W, Poisel S, Hafez ESE. Functional anatomy of the human vagina. En: Hafez SE, Evans TN, editores. *The Human Vagina*. Londres, Elsevier; 1978. p.41-53.

<sup>33</sup> Laterjet - Ruiz Liard. *Anatomía Humana*. Buenos Aires: Editorial Médica Panamericana; 1983.

<sup>34</sup> Snell, R.S. *Anatomía clínica para estudiantes de medicina*. 5. ed. Rio de Janeiro, GuanabaraKoogan, 2000.

<sup>35</sup> Sternberg SS. *Histology for Pathologist*. Second ed. Philadelphia: Lippincot-Raven Publishers; 1997.

<sup>36</sup> Geneser F. *Histología*. 3ª ed. Buenos Aires: Editorial Médica Panamericana; 2003.

the lamina propria, which is the connective tissue-rich elastic fibers and nerves, with a few blood vessels.

The muscle layer is formed by smooth muscle fibers that are arranged to circulate in the area attached to the mucosa and longitudinally on the outside, and some of these longitudinal fibers pass cardinal ligaments form. Adventitia consists vascularized connective tissue with copious nerves and venous and lymphatic plexuses<sup>37,38</sup>.

#### f) *Vaginal orifice*

The vaginal opening is surrounded by the hymen. On each side of the duct opening lobby of the greater vestibular gland or Bartholin is located.

#### g) *Vaginal or vulvar vestibule*

It is the portion of the vulva that is located between the labia minora (from the outer surface of the hymen, limiting forward by the frenulum of the clitoris, anterolaterally by the labia majora and posterolaterally by the line of Hart, located in the medial portion of the older) lips<sup>39</sup>. The mucosa of the lobby is similar to vaginal and equally enriched glycogen mucosa, and that is glucogenic epithelium with transitional epithelium of the urethral meatus and the epithelium of excretory ducts of the greater vestibular glands minors and paraurethral<sup>40</sup>.

#### h) *Hymen*

Tissue is a mucous-membrane partially closing the vaginal introitus, vagina separating the vulva loose<sup>41</sup>; connective tissue composed limited by stratified squamous epithelium without stratum corneum in both vaginal and buccal surface.

The hymen is a membranous remnant of the union between the senovaginales bulbs and the urogenital sinus, and drilling during fetal life to make a connection between the vagina and perineum<sup>42</sup>.

#### i) *Glands*

Skene's glands are the two largest paraurethral ducts that empty into the female urethra, prostate rudimentary counterparts, are bilateral and secrete mucoid material with sexual stimulation, used to lubricate the urethral meatus during intercourse<sup>43</sup>. They are responsible for female ejaculation.

Skene's glands are constituted by a pseudostratified columnar epithelium secreting mucosa and drain into ducts lined by transitional epithelium that lead to the sides of the urethral meatus<sup>44</sup>, in number from two to ten.

Bartholin's glands or greater vestibular glands are two tubulosaccular secretory glands, located on each side of the opening of the vagina, in a clockwise position, at four and eight hours. Secrete a mucoid fluid with sexual stimulation, which helps lubricate the labia during intercourse. Originate from the urogenital sinus and are homologous to the bulbourethral glands in males. Its acini are lined by columnar epithelium mucípar. The ducts that drain the gland are lined by columnar epithelium in the beginning, then by epithelium transitional type to finish by squamous-type epithelium at its end and outlet of the posterolateral portion of the lobby, to the inner and posterior surface of the lips minors<sup>45</sup>.

#### j) *Clitoris*

The clitoris is an erectile organ of 2-3 cms in length at its outer major axis, which is located under the urogenital diaphragm, in front of the symphysis pubis and the anterior perineal region in contact with the pubic rami. Is formed by two arcs, right and left, (with a length 12 to 15 cm) that was merged into midline, causing a 90 degrees forward, forming a sensitive rounded tuber (glans of 3 to 4 mm wide and 4-5 mm long: its unique demonstration outside), being part of the vulva<sup>46</sup>, whose roots are hidden below the vulva<sup>47</sup>, and two erectile vestibular bulbs, coated by ischiocavernosus muscles around the sidewalls of the vagina. Histologically enriched with many sensory receptors, and subject to the pubis by the suspensory ligament<sup>48</sup>. The pillars contain similar penile corpora cavernosa, cavernous veins surrounded by longitudinal muscular smooth muscle and small arteries in the central portion of the erectile tissue<sup>49</sup>. Tunica albuginea is one, outside of this there is loose connective tissue with abundant nerves in the periphery of the columns. The clitoral glans is covered by squamous epithelium which is continuous with the vestibular. In the clitoris are not glands or papillae, but a large number of free nerve endings and

<sup>37</sup> Gartner, L.P., Hiatt, J.L. Texto y atlas de histología. Ed. McGraw Hill-Interamericana, 2002.

<sup>38</sup> Stevens, A., Lowe J. Histología Humana, 3ª ed. Ed. Mosby-Doyma 2006.

<sup>39</sup> Burrows LJ, Shaw HA, Goldstein AT. The vulvar dermatoses. J Sex Med. Feb; 5(2):276-83. Epub 2008 Jan 2. Review. 2008.

<sup>40</sup> Calandra D, di Paola G, Gómez Rueda N, Baliña LM. Enfermedades de la vulva. Buenos Aires: Editorial Médica Panamericana; 1979.

<sup>41</sup> Testut, L. & Latarjet, A. Tratado de anatomía humana. 9ª ed. Madrid, Salvat, 1954. pp.1331-5. Tomo IV.

<sup>42</sup> Stelling JR, Gray MR, Davis AJ, Cowan JM, Reindollar RH. Dominant transmission of imperforate hymen. Fertil Steril 2000; 74 (6): 1241.

<sup>43</sup> Sharif-Aghdas F, Ghaderian N. Female paraurethral cysts: Experience of 25 cases. BJU International 2003;93:353-6.

<sup>44</sup> Geneser F. Histología. 3ª ed. Buenos Aires: Editorial Médica Panamericana; 2003.

<sup>45</sup> Calandra D, di Paola G, Gómez Rueda N, Baliña LM. Enfermedades de la vulva. Buenos Aires: Editorial Médica Panamericana; 1979.

<sup>46</sup> O. Buisson, "Le point G ou l'absence de m'edecinesexuellef'eminine," Gyn'ecologieObst'etricque&Fertilite, vol. 38, no. 12, pp. 781-784, 2010.

<sup>47</sup> V. Puppo, "Embryology and anatomy of the vulva: the female orgasm and women's sexual health," European Journal of Obstetrics Gynecology and Reproductive Biology, vol. 154, no. 1, pp. 3-8, 2011.

<sup>48</sup> V. Puppo, "Re: clitoral anatomy in nulliparous, healthy, premenopausal volunteers using unenhanced magnetic resonance imaging," Journal of Urology, vol. 175, no. 2, pp. 790-791, 2006.

<sup>49</sup> V. Puppo, "Sexually responsive vascular tissue of the vulva," BJU International, vol. 98, no. 2, pp. 463-464, 2006.

countless corpuscles Pacinian and Krause are located ( between 8 and 10 thousand nerve endings ) as it is supplied by one of the three terminal branches of the nerve pudendal, the dorsal nerve of the clitoris<sup>50,51</sup>.

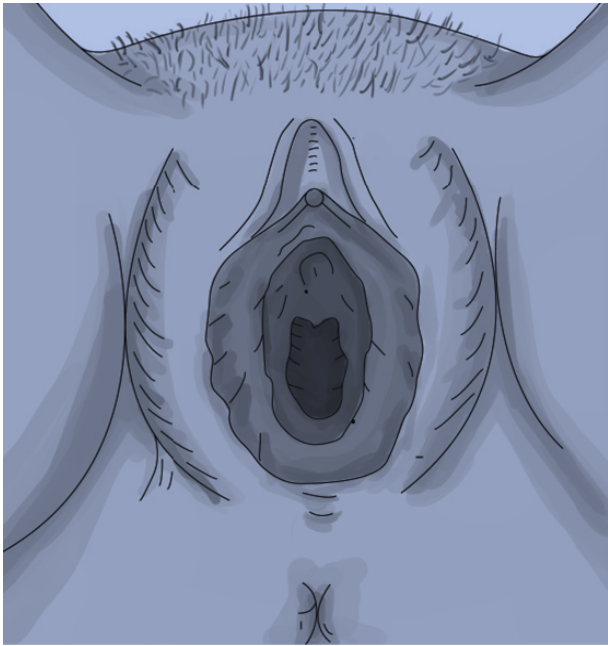


Figure 4 : Structural vulvar

k) *Clitoral complex: complex vagina, clitoris and urethra*

The distal vagina has different properties than the proximal vagina, reflecting their different embryological origins urogenital sinus and Müllerian duct, there is also variation in the structure of the walls, since the side walls are much different from the rear wall, and naturally prior<sup>52</sup>.

The distal vagina is interrelated with the clitoris, so I doubt the two being separated as sexually functional complex structures, but from an anatomical point of view, on the side of the anterior vaginal wall (the mucosa) depth is only clitoris, so I dare say that there is no anatomical relationship between the two, but if you must have an important sensory functional relationship between the two, knowing their embryological origin.

The anterior vaginal wall is separated from the posterior urethral wall by urethrovaginal septum, with a thickness of 10 to 12 mm, through the periurethral fascia<sup>53,54</sup>; tissue comprising fibro and a large number of

blood vessels, glands, fibers muscle and nerve endings, which may explain its importance in sexuality, and not in vain spongiosum of the female urethra has been reported in anatomy books<sup>55</sup>, and so much Grafenberg, in 1950, described the analogy female to male urethra, describing seems to be surrounded by erectile tissue like the corpora cavernosa<sup>56</sup>.

The urethral meatus and the distal urethra are surrounded by the erectile tissue of the vestibular bulbs of the clitoris<sup>57</sup>, so Dr. Grafenberg described an erogenous zone located on the anterior wall of the vagina and subsequent studies have correlated the focus of female orgasmic sensitivity are related to the external urethral sphincter<sup>58</sup>, which forces me to think that the urethra anatomically is surrounded by the clitoris to a varying degree, which may explain its major component in sexuality, knowing what innervated richly out the clitoris, and then maybe take importance naciementemente naming point U<sup>59</sup>, present in some women.

The "G-spot" of Ladas, Whipple and Perry doctors, does not correspond to the external urethral sphincter, but the intra-urethral glands, and that stimulation of the pelvic nerve can also occur with stimulation area "G-spot", which correspond to the area of the female prostate gland, which would explain the reports of female ejaculation and orgasm through stimulation of the urethra, a phenomenon that is present in some women<sup>60</sup>. Figure 5.

<sup>54</sup> R. Putz and R. Pabst, Sobotta Atlas of Human Anatomy, Urban Fischer-Elsevier, Munchen, Germany, 14th edition, 2008.

<sup>55</sup> G. Chiarugi and L. Bucciante, Istituzioni di Anatomia dell'Uomo, Casa editrice Dr. Francesco Vallardi-Societ`a Editrice Libreria, Milano, Italy, 11th edition, 1975.

<sup>56</sup> E. Grafenberg, "The role of urethra in female orgasm," International Journal of Sexology, vol. 3, pp. 145-148, 1950.

<sup>57</sup> H. E. O'Connell, N. Eizenberg, M. Rahman, and J. Cleeve, "The anatomy of the distal vagina: towards unity," Journal of Sexual Medicine, vol. 5, no. 8, pp. 1883-1891, 2008.

<sup>58</sup> G. L. Gravina, F. Brandetti, P. Martini et al., "Measurement of the thickness of the urethrovaginal space in women with or without vaginal orgasm," Journal of Sexual Medicine, vol. 5, no. 3, pp. 610-618, 2008.

<sup>59</sup> Desmond Morris, *The Naked Woman: A Study of the Female Body*, Jonathan Cape, London (2004).

<sup>60</sup> B. R. Komisaruk, C. Beyer-Flores, and B. Whipple, *The Science of Orgasm*, The Johns Hopkins University Press, Baltimore, Md, USA, 2006.

<sup>50</sup> Hollabaugh RS Jr, Steiner MS, Sellers KD, Samm BJ, Dmochowski RR. Neuroanatomy of the pelvis: implications for colonic and rectal resection. *Dis Colon Rectum* 2000; 43: 1390-7.

<sup>51</sup> Shafik A, Doss SH. Pudendal canal: surgical anatomy and clinical implications. *Am Surg* 1999; 65: 176-80.

<sup>52</sup> H. E. O'Connell, N. Eizenberg, M. Rahman, and J. Cleeve, "The anatomy of the distal vagina: towards unity," *Journal of Sexual Medicine*, vol. 5, no. 8, pp. 1883-1891, 2008.

<sup>53</sup> F. H. Netter, *Atlas of Human Anatomy*, Saunders-Elsevier, Philadelphia, Pa, USA, 5th edition, 2010.

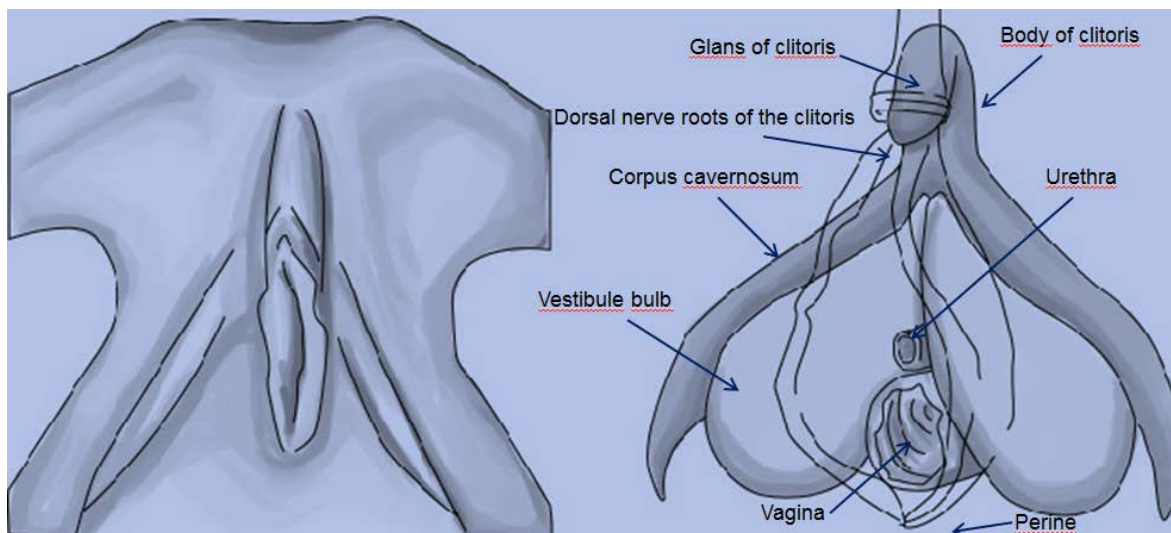


Figure 5: Vagina Complex, clitoris and urethra

#### IV. CONCLUSIONS

Sexual pleasure is a right we all have, and women must find a way to feel or experience orgasm as a possible experience of their sexuality, which necessitates effective stimulation.

Scientists and sexologists should define how relevant is whether or not the controversial "G-spot", but in my opinion, whether or not there is irrelevant. The woman who you found should use it and enjoy at will, and those that are not found, I invite you to try not to stop, not just look into the vagina, for it is in this search that can get to know enough to know what area or corner of your body, which is located its point of maximum pleasure.



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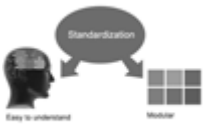


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**5. Ask your Guides:** If you are having any difficulty in your research, then do not hesitate to share your difficulty to your guide (if you have any). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work then ask the supervisor to help you with the alternative. He might also provide you the list of essential readings.

**6. Use of computer is recommended:** As you are doing research in the field of Computer Science, then this point is quite obvious.

**7. Use right software:** Always use good quality software packages. If you are not capable to judge good software then you can lose quality of your paper unknowingly. There are various software programs available to help you, which you can get through Internet.

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**9. Use and get big pictures:** Always use encyclopedias, Wikipedia to get pictures so that you can go into the depth.

**10. Bookmarks are useful:** When you read any book or magazine, you generally use bookmarks, right! It is a good habit, which helps to not to lose your continuity. You should always use bookmarks while searching on Internet also, which will make your search easier.

**11. Revise what you wrote:** When you write anything, always read it, summarize it and then finalize it.





**12. Make all efforts:** Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

**13. Have backups:** When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

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**15. Use of direct quotes:** When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

**16. Use proper verb tense:** Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

**17. Never use online paper:** If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

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**19. Know what you know:** Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

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**21. Arrangement of information:** Each section of the main body should start with an opening sentence and there should be a changeover at the end of the section. Give only valid and powerful arguments to your topic. You may also maintain your arguments with records.

**22. Never start in last minute:** Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

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**24. Never copy others' work:** Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

**25. Take proper rest and food:** No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

**26. Go for seminars:** Attend seminars if the topic is relevant to your research area. Utilize all your resources.



**27. Refresh your mind after intervals:** Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

**28. Make colleagues:** Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

**29. Think technically:** Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

**30. Think and then print:** When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

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**33. Report concluded results:** Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

**34. After conclusion:** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

## INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

### Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

### Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.



Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

### **General style:**

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

- Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

- Use standard writing style including articles ("a", "the," etc.)
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- Use paragraphs to split each significant point (excluding for the abstract)
- Align the primary line of each section
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- Use present tense to report well accepted
- Use past tense to describe specific results
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- Shun use of extra pictures - include only those figures essential to presenting results

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Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.



## Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript-- must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for brevity. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

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- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

## Approach:

- Single section, and succinct
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- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
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- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

## Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.



- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
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- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

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- Report the method (not particulars of each process that engaged the same methodology)
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- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

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- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

#### **What to keep away from**

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
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The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently. You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.





## Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

### What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
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- Never confuse figures with tables - there is a difference.

### Approach

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- Put figures and tables, appropriately numbered, in order at the end of the report
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- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

### Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
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<i>Methods and Procedures</i>	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
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<i>Discussion</i>	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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