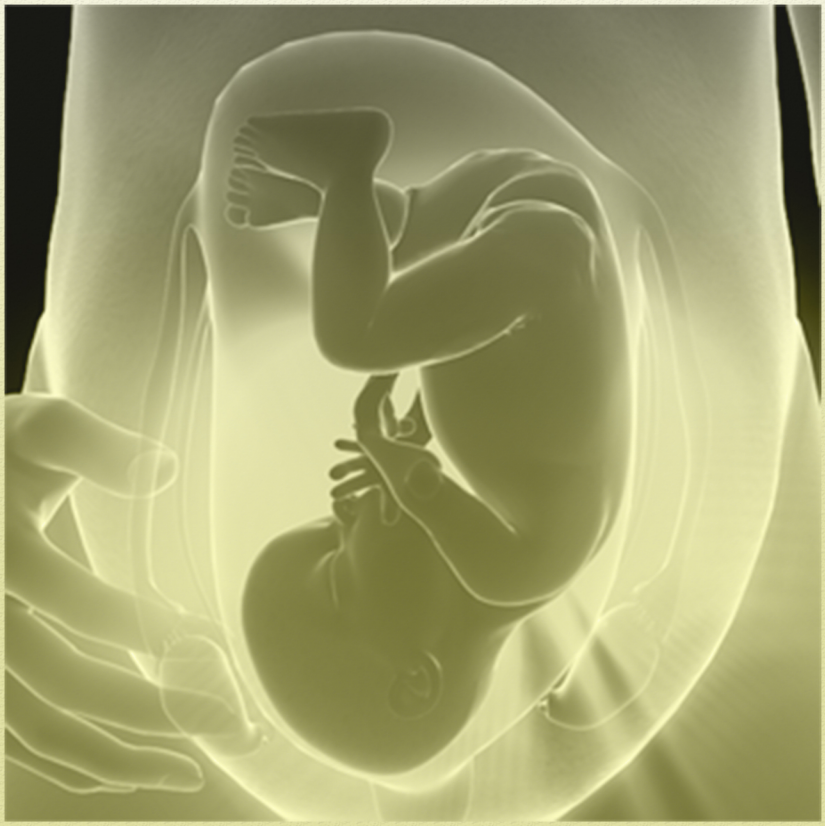
September, 2015 ● Volume 2, Issue 3

Openventio PUBLISHERS

ISSN 2377-1542



GYNECOLOGY AND OBSTERICS RESEARCH

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GYNECOLOGY AND OBSTETRICS RESEARCH

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ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-e003

Editorial

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Volume 2 : Issue 3
Article Ref. #: 1000GOROJ2e003

Article History:
Received: July 7th, 2015
Accepted: July 10th, 2015
Published: July 13th, 2015

Citation:
Parasar P. Endometriosis research: need for a stem-cell based experimental model. *Gynecol Obstet Res Open J*. 2015; 2(3): e6-e8.

Endometriosis Research: Need for a Stem-Cell Based Experimental Model

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ABSTRACT

Endometriosis is a complex disease and not a single phenotype can be delineated in available *in vitro* models. A comparative analysis of pluripotent stem cells in normal endometrium and endometriosis will give an understanding of status of biomarkers in endometrium and endometriosis, respectively. Highly pluripotent stem cells are critically important constituents of endometrium and contribute to ectopic endometriotic implants as reported in various studies. Because stem cells are undifferentiated and possess tremendous regenerative capacity, they are candidate cellular system for modeling endometriosis.

KEYWORDS: Endometriosis; Stem cells; Experimental model.

INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma like lesions outside of the uterus. A unique feature of the menstrual cycle in women and non-human primates is the retrograde menstruation – an outflow of the endometrial lining through the patent fallopian tubes into the pelvic space.[1] This retrograde flow, along with potential hematogenous or lymphatic circulation,[2] results in the seeding of endometrial tissue in ectopic sites. Endometrial and bone marrow-derived stem cells are progenitor cells which differentiate into endometrium and also contribute to ectopic endometrium.[3,4] These implants often persist for several years and result in consequent pelvic pain, infertility and inflammation.[5] Patients often present with other associated symptoms, including dysmenorrhea, dyspareunia, dyschezia and dysuria.[5,6] Endometriosis is a highly debilitating disease,[7] affecting 5-10% of all women of reproductive age[4-6,8] and 35-50% women with pelvic pain and infertility impacting quality of life.[7,9] The majority of women present symptoms in adolescence, but average delay to diagnosis is 7 years.[7,10,11] Clinical studies also report that endometriosis patients have increased risk for autoimmune diseases and ovarian cancer.[12]

Treatment options for endometriosis patients are limited to surgery, hormone therapy and analgesics.[6] No gene-targeted medical therapies exist to date, likely due to the fact that definitive pathogenesis-mechanisms of endometriosis are yet to be determined.

Structure of the Human Endometrium

Endometrium is the inner mucosal lining of the uterus consisting primarily of two types of cells - the epithelial cells of the glands and lumen (the glandular and luminal epithelial cells) and the mesenchymal (stromal) cells. Other supporting mesenchymal cells are endothelial cells, fibroblasts and leukocytes. Endometrial glands are indistinctly separated from the underlying smooth muscle layer of the myometrium in the absence of submucosal tissue. Endometrium is functionally divided into two layers. The outer functionalis layer comprises the upper two-thirds and is composed of dense glandular tissue and loose connective stroma. The inner basalis layer rests on the subendometrial myometrium and contains the base of glands,

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-e003

dense stroma, large vessels, and germinal cells that help generate the new functionalis each month after menstrual shedding of the upper functionalis and partial basalis.[3]

Theories of Endometriosis

Definitive etiopathogenetic mechanisms of endometriosis are yet to be discovered although exploration into genetic predisposition,[13,14] polymorphism in mitochondrial DNA, and altered immune response is ongoing.[6] Endometriosis can result from either primary or secondary retrograde menstruation,[2] the latter being a result of the congenital obstruction of the menstrual tract as seen in congenital Müllerian anomalies.

Retrograde menstruation theory is the most accepted theory of endometriosis.[2] Another theory proposed for the pathophysiology of endometriosis includes coelomic metaplasia, which explains that mesothelial cells in peritoneum differentiate into endometrial tissue.[15] Aberrant molecular and/or biochemical pathways in endometrium and overproduction of estrogens, cytokines, prostaglandins, and metalloproteinases due to abnormal biosynthetic pathways may also stimulate the migration of endometrial implants into ectopic sites. Immunological failure to get rid of these migrants sets up the establishment of implants.[5,6] Stem cells from endometrial tissues and bone marrow have been demonstrated to migrate the ectopic endometrial tissue implants.[3,4] Consequently endometriosis is multifactorial and polygenic in nature.

Stem Cells in Endometriosis

Stem cells are highly self-renewable, primitive unspecialized cells which undergo differentiation to produce a vast array of specialized cells with minimal or no differentiation capacity. Therefore, stem cells are invaluable tools to develop disease models and to study the mechanism of pathogenesis of a disease as well as to test the drugs and therapy for a disease.[16] Genetic factors underlying a disease, detected in stem cell disease models, can thus be used as potential targets for drugs. Obtaining diseased cells, in many diseases, is a challenge, therefore, entails generation of an *in vitro* model to test novel therapeutic drugs and gene editing therapies in order to rectify the dysfunction of cells in a disease. Stem cells from diseased individual can be retrieved and differentiated in diseased cells with diseased phenotype. Alternatively, diseased cells can also be reprogrammed to generate Induced Pluripotent Stem Cells (IPSCs) to *in vitro* differentiate into large quantity of diseased cells. In both cases, characteristic phenotype of a disease can be investigated to study mechanism of pathogenesis of disease.

Endometrium is highly regenerative tissue. With each menstruation cycle, functionalis layer is shed and subsequently regenerated. The regenerative capacity of endometrium lies in the highly renewable and pluripotent adult stem or progenitor cells present in the basalis region.[17] Endometrial stem cells can differentiate into chondrocytes, adipocytes, smooth muscle cells and osteoblasts.[18] Partial shedding of the basalis region with each retrograde menstruation may lead to migration of endometrial stem cells and adult progenitor cells, which suggests that basalis layer and the inhabitant cells are potential contributors to endometriotic lesions. Studies have found an increased number of fragments of the shed basalis layer in the menstrual blood of women with endometriosis as compared to healthy controls. This suggests that basalis layer and its endometrial stem cells play an important role in endometriosis. Not only endometrial progenitor cells, but also hematopoietic stem cells has been purportedly involved in contribution of endometriosis.[19] These undifferentiated stem cells from endometrium and endometriosis can be useful tool to study the molecular pathogenetic mechanism of endometriosis and hence infertility.

Need to Identify Biomarkers of Endometriosis

Endometriosis is the disease of menstruating species primarily humans and some non-human primates. At the time of clinical presentation, most women have endometriosis, therefore, possess no experimental evidence of physiological role in pathogenesis of endometriosis. Monitoring of progression requires repeated laparoscopies and thus controlled experiments in humans are limited due to ethical reasons and cost of handling. Definitive diagnosis of multifactorial endometriosis requires a surgical procedure. Therefore, patients suffer for several years until appropriate treatment is obtained. In order to facilitate an earlier stage diagnosis, identification of a specific biomarker which would indicate normal and pathogenic processes of disease progression is greatly needed. Studies have revealed the role of glycoproteins, inflammatory and non-inflammatory cytokines, adhesion molecules, and angiogenic and growth factors in pathogenesis and development of endometriotic lesions.[6] Other studies have isolated subpopulations of endometrial stromal and glandular cells which express characteristic genetic markers CD13 and CD9, respectively and regenerate into endometrium *in vitro*.[20] However, neither a single biomarker nor a panel of biomarkers has been proven to be a reliable non-invasive tool for endometriosis. A convenient experimental model is vital to study the pathophysiological mechanisms of development of endometriosis. In addition, an *in vitro* model of endometriosis would be instrumental to develop and test therapeutic strategies to prevent the onset and progression of endometriosis.

REFERENCES

1. Finn CA. Why do women and some other primates menstruate? *Perspect Biol. Med.* 1987; 30(4): 566-574.

2. Sampson JA. Metastatic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation. *Am. J. Pathol.* 1927; 3(2): 93-110.

3. Sasson IE, Taylor HS. Stem cells and the pathogenesis of

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-e003

endometriosis. *Ann N Y Acad. Sci.* 2008; 1127: 106-115. doi: 10.1196/annals.1434.014

4. Figueira PG, Abrão MS, Krikun G, Taylor HS. Stem cells in endometrium and their role in the pathogenesis of endometriosis. *Ann N Y Acad Sci.* 2011; 1221(1): 10-17. doi: 10.1111/j.1749-6632.2011.05969.x

5. Giudice LC, Kao LC. Endometriosis. *Lancet.* 2004; 364(9447): 1789-1799.

6. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. *Nat. Rev. Endocrinol.* 2014; 10(5): 261-275. doi: 10.1038/nrendo.2013.255

7. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril.* 2011; 96(2): 366-373. doi: 10.1016/j.fertnstert.2011.05.090

8. Bruner-Tran KL, Herington JL, Duleba AJ, Taylor HS, Osteen KG. Medical management of endometriosis: emerging evidence linking inflammation to disease pathophysiology. *Minerva Ginecol.* 2013, 65(2): 199-213.

9. De Graaf AA, D'Hooghe TM, Dunselman GA, et al. The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey. *Hum. Reprod.* 2013; 28(10): 2677-2685. doi: 10.1093/humrep/det284

10. Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. *J. Pediatr. Adolesc. Gynecol.* 1997; 10(4): 199-202. doi: 10.1016/S1083-3188(97)70085-8

11. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am. J. Epidemiol.* 2004; 160(8): 784-796. doi: 10.1093/aje/kwh275

12. Vercellini P, Somigliana E, Buggio L, Bolis G, Fedele L. Endometriosis and ovarian cancer. *Lancet Oncol.* 2012; 13(5): e188-e189.

13. Painter JN, Anderson CA, Nyholt DR, et al. Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis. *Nat. Genet.* 2011; 43(1): 51-54. doi: 10.1038/ng.731

14. Rahmioglu N, Nyholt DR, Morris AP, Missmer SA, Montgomery GW, Zondervan KT. Genetic variants underlying risk of endometriosis: insights from meta-analysis of eight genome-wide association and replication datasets. *Hum. Reprod. Update.* 2014; 20(5): 702-716. doi: 10.1093/humupd/dmu015

15. Ferguson BR, Bennington JL, Haber SL. Histochemistry of mucosubstances and histology of mixed müllerian pelvic lymph node glandular inclusions. Evidence for histogenesis by müllerian metaplasia of coelomic epithelium. *Obstet. Gynecol.* 1969; 33(5): 617-625.

16. Sterneckert JL, Reinhardt P, Schöler HR. Investigating human disease using stem cell models. *Nat Rev Genet.* 2014; 15(9): 625-639. doi: 10.1038/nrg3764

17. Padykula HA, Coles LG, Okulicz WC, et al. The basalis of the primate endometrium: a bifunctional germinal compartment. *Biol. Reprod.* 1989; 40(3): 681-690. doi: 10.1095/biolreprod40.3.681

18. Gargett CE, Chan RW, Schwab KE. Endometrial stem cells. *Curr. Opin. Obstet. Gynecol.* 2007; 19(4): 377-383.

19. Du H, Taylor HS. Contribution of bone marrow-derived stem cells to endometrium and endometriosis. *Stem Cells.* 2007; 25(8): 2082-2086. doi: 10.1634/stemcells.2006-0828

20. Deane JA, Gualano RC, Gargett CE. Regenerating endometrium from stem/progenitor cells: is it abnormal in endometriosis, Asherman's syndrome and infertility? *Curr Opin Obstet Gynecol.* 2013; 25(3): 193-200. doi: 10.1097/GCO.0b013e32836024e7

GYNECOLOGY AND OBSTETRICS RESEARCH

Openventio PUBLISHERS

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-e004

Editorial

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Volume 2 : Issue 3
Article Ref. #: 1000GOROJ2e004

Article History:
Received: August 28th, 2015
Accepted: August 31st, 2015
Published: September 1st, 2015

Citation:
Brownbill P. Human placentas and the changing face of reproductive toxicology testing. *Gynecol Obstet Res Open J*. 2015; 2(3): e9-e10.

Human Placentas and the Changing Face of Reproductive Toxicology Testing

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KEYWORDS: Placenta; Perfusion; Models; Reproductive; Toxicology; Testing; Animal.

Pharmaceuticals are in use by 40-98% of pregnant mothers in the developed world, varying by country. There is a significant potential for obstetricians to further maintain medical prescriptions for chronic diseases during pregnancy, provided there is confidence within the pharmaceutical industry on the safety of their products. The safety of medicinal products incurs several socioeconomic challenges, and the protection of maternal and fetal health is a foremost and top priority. Current guidelines for reproductive toxicity testing in rats and rabbits provide the required data for international regulatory bodies, such as the Federal Drug Agency (FDA) and the European Medicines Agency (EMA) and are described by the Organization for Economic Cooperation and Development (OECD). These animal studies include fetal organ anthropometry, but are devoid of much fetal organ functional data, so there is a case for improving animal data quality during reproductive toxicity testing. Human placental models have a real potential to refine, or even replace some animal use in the pharmaceutical industry, by predicting the probability of unfavourable events for fetal growth and development and highlighting additional specific outcome measures to be used in rat and rabbit reproductive toxicology testing.

The pharma industry is engaging in a new drive for a revision of the regulations to include [new] "opportunities for modernising testing paradigms to enhance human risk assessment, while also potentially reducing animal use" (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH(S5) guidelines). In a recently published concept paper, the ICH consider the "development of basic principles for possible regulatory acceptance of *in vitro, ex vivo* and non-mammalian *in vivo* EFD assays". There has been a general recent discussion surrounding the values of alternatives to animal testing,[1,2] including a streamlined high-tech approach of developing an "organ on a chip".[3,4] These alternative methods would add an additional weight of evidence to pharma's *reproductive risk assessment protocols* prior to the inclusion studies of *Women of Child Bearing Potential* in clinical trials. In response to this call, the use of human placental models in safety evaluation may soon be on the horizon.

The placenta is orchestrated to respond to fetal needs during its growth and development. Whilst new emerging technology using zebra fish larvae is furnishing useful teratological assessments prior to the use of more complex *in vivo* mammalian models, this model lacks a placenta, therefore missing potential effects of pharmaceuticals on placental nutrient accretion, endocrinology, metabolism, xenobiotic transfer and haemodynamics; facets which have to be understood prior to the administration of a compound to a pregnant woman. A testing platform of theoretical (analytical and computational) and human placental experimental models could help bridge this information gap, ultimately helping obstetricians guide pregnant women who take medication for their chronic medical conditions.

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-e004

A momentum is building within Europe, developed by an association called *PlaNet* (placentology network), comprising of 25 EU centres from 15 countries with academic, clinical, industrial, standardisation and policy making backgrounds. Their academic expertise includes obstetrics, physiology, pharmacology, biophysics and mathematical modellers. *PlaNet's* objectives are to help provide better advice on the safety of medicinal products and environmental substances in pregnancy, create a pool of standards for human placenta toxicology test systems and explore the potential to deliver both cost savings and reductions in the number of animals used in reproductive toxicology safety testing. An evaluation of human placenta research systems is central to this initiative. Human placental tissue from a range of gestational ages is readily available to researchers with informed consent, where there is an established association with the Obstetric and Gynaecology Department. Proposed human placental test systems vary widely from the use of more simplistic placental barrier microvillous membrane vesicles, manufactured from the maternal blood-facing syncytiotrophoblast epithelium; to the most complex human *ex vivo* dual placental cotyledon perfusion model, most notably developed by Prof. Henning Schneider in the late 1960's/early 1970's and being continually enhanced today; most recently, to appropriate oxygenation to an unusually low normal soluble level found in this tissue *in utero*. A platform of human placental test systems has the potential to deliver meaningful data relating to xenobiotics transfer rates, uptake and pharmacokinetics; changes in nutrient and ion uptake; permeability dysregulation; alterations to endothelial and trophoblast signalling; fetoplacental vascular blood flow and resistance changes; disruption to placental angiogenesis and vasculogenesis; changes in paracrine signalling and placental barrier signal transduction; inflammation and immune modulation; trophoblast invasion and implantation; syncytiotrophoblast shedding commonly associated with the pathology of preeclampsia; DNA damage and repair; genotoxicity and carcinogenesis risk indicators. What is more, the human placenta is a unique organ, differing significantly from placentas of other species, both in structure and in function. Thus, the human placenta-based experimental and theoretical techniques have potential not only to refine and reduce the animal use in reproductive toxicological research, but also to strengthen the relevance of derived conclusions.

This moment of global rethinking on reproductive toxicity testing guidance appears to be a fitting juncture to consider standardising a human placental testing platform across research institutes internationally. It presents a real and exciting opportunity to develop mathematical modelling tools related to human placental function that will assist in our understanding of important factors such as xenobiotics transfer to the human fetus, their toxicological effects on nutrient and oxygen transfer and potential effects on placental haemodynamics, which could impinge on fetal growth and development. Most importantly, the time is ripe for academic researchers to engage with the pharma industry, which is currently challenged with slowing growth, but also outwardly looking for reinvention opportunities.

REFERENCES

1. Burden N, Sewell F, Chapman K. Testing chemical safety: what is needed to ensure the widespread application of non-animal approaches? *PLoSBiol*. 2015; 13: e1002156. doi: 10.1371/journal.pbio.1002156

2. Willyard C. The boom in mini stomachs, brains, breasts, kidneys and more. *Nature*. 2015; 523: 520. doi: 10.1038/523520a

3. Reardon S. 'Organs-on-chips' go mainstream. *Nature*. 2015; 523: 266. doi: 10.1038/523266a

4. Esch EW, BahinskiA, Huh D. Organs-on-chips at the frontiers of drug discovery. *Nat Rev Drug Discov*. 2015; 14: 248-260. doi: 10.1038/nrd4539

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ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-114

Research

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Volume 2 : Issue 3
Article Ref. #: 1000GOROJ2114

Article History:
Received: June 20th, 2015
Accepted: July 16th, 2015
Published: July 20th, 2015

Citation:
Moniem AMA, Abdelrazak KM, Hussain M, Awadalla AM, Abdelazim IA. Outcomes and accuracy of 2D gray-scale ultrasound scan in prenatal diagnosis of morbid adherent placenta. *Gynecol Obstet Res Open J*. 2015; 2(3): 62-68.

Outcomes and Accuracy of 2D Gray-Scale Ultrasound Scan in Prenatal Diagnosis of Morbid Adherent Placenta

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ABSTRACT

Objective: This study designed to evaluate outcomes and accuracy of 2D gray-scale ultrasound scan in prenatal diagnosis of Morbid Adherent Placenta (MAP).
Patients and methods: Fifty pregnant women ≥28 weeks gestation with suspected MAP studied. 2D trans-abdominal gray-scale ultrasound scan done for studied women to confirm; placental location and findings suggestive of MAP. Intra-operative findings at delivery compared with pre-operative sonographer findings to evaluate outcomes and accuracy of 2D gray-scale ultrasound scan in prenatal diagnosis of MAP.
Results: 56%(28/50) of studied women had difficult placental separation, considerable intraoperative blood loss. Bilateral internal iliac artery ligation done to control bleeding in 28%(14/50), intrauterine compression balloon with placenta bed sutures done in 6%(3/50) and cesarean hysterectomy done in 22%(11/50) of studied women. Best 2D gray-scale ultrasound parameters for detection of difficult placental separation and considerable intraoperative blood loss in studied cases were; abnormal placental lacunae (73.9% sensitivity) and exophytic mass invading bladder (100% specificity & 100% PPV).
Best 2D gray-scale ultrasound parameters for detection of emergency hysterectomy were; disruption of uterine serosa-bladder interface (81.8% sensitivity) and exophytic mass invading bladder (94.9% specificity, 66.7% PPV and 84.1% NPV).
Conclusion: Antenatal diagnosis of MAP is crucial for; proper counseling for possible surgical complications, multidisciplinary team care and recruitment. Best 2D gray-scale ultrasound parameters for detection of difficult placental separation in studied cases were; exophytic mass invading bladder, while, best 2D gray-scale ultrasound parameters for detection of emergency hysterectomy were; disruption of uterine serosa-bladder interface and exophytic mass invading bladder.

KEYWORDS: Outcomes; 2D gray-scale ultrasound; Morbid adherent placenta.

ABBREVIATIONS: MAP: Morbid Adherent Placenta; cEBL: calculated Estimated Blood Loss; RBCs: Red Blood Cells; SPSS: Statistical Package for Social Sciences; LMP: Last Menstrual Period.

INTRODUCTION

Placenta accreta occurs when placental trophoblasts invade endometrium beyond the

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ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-114

Nitabuch's layer of decidua basalis, while placenta increta occurs when placental trophoblasts invade myometrium and placenta percreta occurs when trophoblasts invade serosa.[1,2]

MAP (morbid adherent placenta) is usually associated with excess blood loss, bladder injuries and hysterectomies.[3,4] Incidence of MAP has increased significantly over the past 50 years.[5,6]

Previous cesarean delivery, placenta previa and damage of Nitabuch's layer of decidua basalis following intrauterine infection or scarring are risk factors of MAP.[1,7-9] Incidence of MAP is increased concomitantly with increased cesarean section rates.[1,7-9]

Incidence of MAP is 3.3% in pregnant women with no prior cesarean delivery and placenta previa and is 40% in pregnant women with previous two cesarean sections and placenta previa.[4] If MAP was diagnosed or suspected before delivery, the optimum time for planned delivery is around 34-35 weeks following a course of corticosteroid and multidisciplinary care team approach.[2,10,11]

Accurate diagnosis of MAP is essential to prepare both patient and health providers for possible complications during delivery. Authors reported that ultrasound is a useful tool to diagnose MAP with 77-93% sensitivity and 71-98% specificity and MRI should be reserved for cases with inconclusive sonographic findings.[12-17]

Prenatal diagnosis of MAP allows development multidisciplinary care team approach during delivery.[14] This study aimed to detect outcomes and accuracy of 2D gray-scale ultrasound scans in prenatal diagnosis of morbid adherent placenta (MAP).

PATIENTS AND METHODS

From February 2011 to February 2015, pregnant women ≥28 weeks gestation with placenta previa anterior covering scar of previous cesarean section scar by trans-abdominal gray-scale ultrasound scan were included in this study conducted in Ain Shams University Maternity Hospital, Cairo, Egypt, after approval of ethical committee. Thorough history and examination of all studied women was followed by 2D trans-abdominal gray-scale ultrasound scan to confirm; gestational age, placental location, findings suggestive of MAP. Findings suggestive of MAP by 2D gray-scale ultrasound scan were;

1. Obliteration of clear space between uterus and placenta, (Figure 1).
2. Visualization of placental lacunae (irregular vascular spaces), moth-eaten appearance placenta (Figure 1).
3. Interruption of posterior uterine serosa-bladder interface.
4. Exophytic mass invading bladder.[11,18]

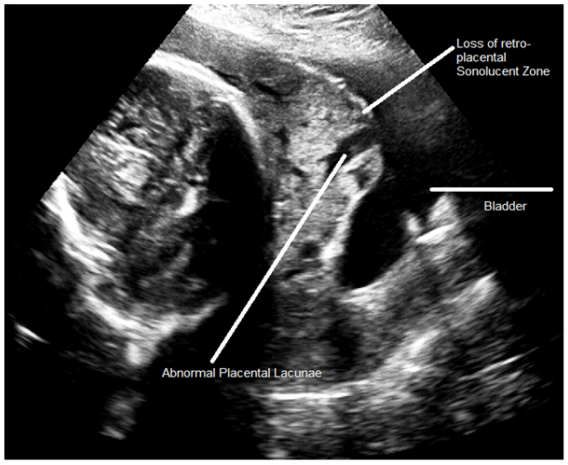

Figure 1: 2D gray scale ultrasound scan shows loss of retro-placental sonolucent zone and abnormal placental lacunae in morbid adherent placenta.

All scans were done for all studied women in supine position with sufficient and comfortably bladder volume to allow optimal visualization of uterine serosa-bladder interface. Ultrasound scans were done by sonographer who was blinded to patient`s criteria using Medision machine (Sonoace X8, Medison Co, South Korea) with 4-7 Mhz (Megahertz) multi-frequency convex probe. Gestational age was calculated from first day of Last Menstrual Period (LMP) and confirmed by early ultrasound done at 20th weeks gestation.

According to Ain Shams University Maternity Hospital protocol, all studied women were hospitalized at 32 weeks and delivered at 35 weeks, following a course of corticosteroids. Emergency cesarean section was done if significant bleeding developed before time of planned cesarean section. All deliveries were conducted in attendance of obstetrics and anesthetic consultants on duty and urologist on duty was informed in case bladder injury or reconstruction was needed.[2-10] A written consent was taken from all studied women explaining; possible intra-operative complications (blood transfusion, hysterectomy, internal iliac ligation) and postoperative complications (deep venous thrombosis, prolonged hospital stay and intensive care unit admission). Women included in this study were also, cross matched with fresh frozen plasma and packed RBCs (Red Blood Cells). Intra-operative findings including; difficulty in placental separation, degree of placental invasion (superficial myometrial invasion or deep myometrial invasion to uterine serosa), bleeding from placental site, amount of blood loss, intraoperative blood transfusion recorded. Also, need for internal iliac ligation or emergency hysterectomy to control bleeding and histopathology results of removed uteri in cases managed by emergency hysterectomy recorded.[19] cEBL (calculated Estimated Blood Loss) was evaluated using Stafford, et al. formula.[20] Intra-operative findings (Figure 2) were compared with pre-operative sonographer findings to evaluate accuracy of 2D gray-scale ultrasound scans in prenatal diagnosis of MAP.

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-114

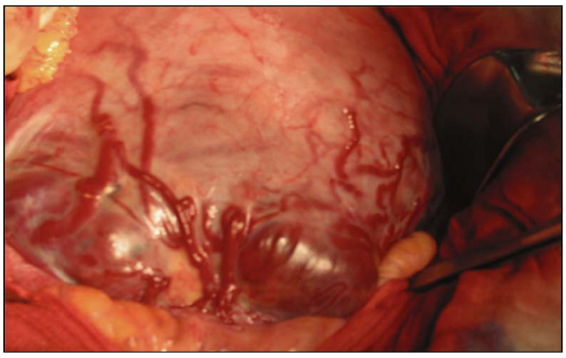

Figure 2: Intraoperative findings of a case of MAP with numerous vessels over uterine serosa and confirmed as placenta percreta after hysterectomy.

SAMPLE SIZE AND STATISTICAL ANALYSIS

Using data from previous studies and EpiInfo® version 6.0, a sample size of 50 women was needed to produce a significant difference. Data were collected and statistically analyzed using SPSS (Statistical Package for Social Sciences); computer software version 18 (Chicago, IL, USA). Mean and SD (standard deviation) were used to represent numerical variables, while, number and percentage were used to represent categorical variables. Student's t and Mann-Whitney's tests were used for analysis of quantitative data, Chi-square (X^2) test for analysis of qualitative data and regression analysis to predict outcomes of categorical dependent variables. P value <0.05 was considered significant, also, sensitivity, specificity and predictive values of ultrasound diagnostic criteria of MAP were calculated.

RESULTS

Demographic data of 50 studied women with suspected MAP were represented in Table 1.

56%(28/50) of studied women had difficult placental separation, considerable blood loss (≥1500 cc) and received blood transfusion. Bilateral internal iliac artery ligation done to control bleeding in 28%(14/50) of studied women, intrauterine compression balloon with placenta bed sutures done in 6% (3/50) of studied women and cesarean hysterectomy done in 22%(11/50) of studied women. Histopathological examination of surgically removed uteri showed; placenta accreta in 10%(5/50) cases, placenta increta in 8%(4/50) cases and placenta percreta in 4%(2/50 cases). 10%(5/50) cases of bladder injury were recorded during this study. (Table 1)

Number of cesarean deliveries (median 3 (1-4 range) *versus* 1 (1-2 range); respectively) and parity (median 4 (1-6 range) *versus* 1 (1-2 range): respectively) were high among women, who had difficult placental delivery, women who had considerable intraoperative blood loss and women required emergency hysterectomy to control bleeding. (Table 2)

All 2D gray scale ultrasound parameters (except abnormal placental lacunae) were significantly high in women who had difficult placental separation and considerable intraoperative blood loss and emergency hysterectomy compared with women who did not have difficult placental separation or considerable blood loss. (Tables 3 and 4)

Variables	Total Number of studied women=50
Age (years)	31.22±4.82*
Duration from last cesarean section (years)	3.4±2.39*
Gestational age at scan (weeks)	30.6±3.17*
Gestational age at delivery (weeks)	34.7±1.2*
Preoperative hematocrit	30.8±3.3*
48-hours postoperative hematocrit	27.3±4.1*
Postoperative hematocrit drop	3.4 ± 2.4*
Considerable intraoperative blood loss (≥1500 cc)	28(56%)**
Intraoperative blood transfusion	28(56%)**
Easy placental separation Difficult placental separation	22(44%)** 28(56%)**
No need for additional surgical steps Bilateral Internal Iliac Ligation Emergency hysterectomy Intrauterine compression balloon and placental bed sutures	22(44%)** 14(28%)** 11(22%)** 3(6%)**
Histopathology results of surgically removed uteri Placenta accrete Placenta increta Placenta percreta	 5(10%)** 4(8%)** 2(4%)**
Intraoperative bladder injury	5(10%)**

*Data represented as Mean±SD. **Data represented as Number and percentage.

Table 1: Preoperative and intraoperative data of studied women with suspected morbid adherent placenta.

Variables	Women who had difficult placental delivery and considerable intraoperative blood loss and required emergency hysterectomy	Women who did not have difficult placental delivery or considerable intraoperative blood loss or required emergency hysterectomy	P value Significance
Age (years) Mean±SD	30.3±5.2	30.9±4.1	0.13* (NS)
Body Mass Index (BMI), (Kg/m^2) Mean±SD	25.3±3.2	24.7±2.9	0.32* (NS)
Parity Median (Range)	4(1-6)	1(1-2)	0.02** (S)
Number of previous cesarean section Median (Range)	3(1-4)	1(1-2)	0.04** (S)
Gestational age at delivery (weeks) Mean±SD	35.9±1.7	36.2±1.4	0.18* (NS)

*Analysis using independent student's t-test. **Analysis using Mann-Whitney's U-test. NS: Non-Significant; S: Significant

Table 2: Women who had difficult placental delivery, considerable intraoperative blood loss and required emergency hysterectomy to stop bleeding compared with women who did not have difficult placental delivery or considerable blood loss or required emergency hysterectomy to stop bleeding.

Regression analysis showed that; the risk of difficult placental separation and considerable intraoperative blood loss increased; 3 times (95% CI; 1.7-8.5) with irregular retro-placental sonolucent areas, 7 times (95% CI; 1.8-27.2) with disruption

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Variables	Women who had difficult placenta separation and considerable intraoperative blood loss (number=28)	Women who did not have difficult placenta separation or considerable intraoperative blood loss (number=22)	P value Significance RR (95% CI)
2D gray-scale parameters			
Loss of retro-placental sonolucent space	26(92.8%)	7(31.8%)	0.03(S), 2.9(1.5-5.4)
Irregular retro-placental sonolucent area	25(89.3%)	5(22.7%)	0.01(S), 3.0(1.7-8.5)
Disruption of uterine serosa-bladder interface	18(64.3%)	2(9.1%)	0.006(S), 7.0(1.8-27.2)
Exophytic mass invading bladder	8(28.6%)	0(0%)	0.003(S),1.34(0.8-22.1)
Abnormal placental lacunae	21(75%)	14(63.6%)	0.7(NS), 0.39(0.1-0.8)

Data represented as number and percentage. Analysis using Chi-square (X2) test. NS: Non-Significant; S: Significant; 2D: Two Dimensional; RR: Relative Risk; CI: Confidence Interval

Table 3: 2D gray-scale parameters in women who had difficult placental separation and considerable intraoperative blood loss compared with women who did not have difficult placental separation or considerable intraoperative blood loss.

Variables	Women who required emergency hysterectomy (number=11)	Women who did not require hysterectomy (number=39)	P value Significance
2D gray-scale parameters			
Loss of retro-placental sonolucent space	11(100%)	13(33.3%)	0.03(S), 3(1.9-4.6)
Irregular retro-placental sonolucent area	11(100%)	12(30.8%)	0.02(S), 3.2(1.9-4.6)
Disruption of uterine serosa-bladder interface	9(81.8%)	7(17.9%)	0.01(S), 4.5(2.2-33.7)
Exophytic mass invading bladder	4(36.4%)	2(5.1%)	0.02(S), 7.1(1.4-33.7)
Abnormal placental lacunae	8(72.7%)	26(66.7%)	0.8(NS), 1.1(0.7-1.6)

Data represented as number and percentage. Analysis using Chi-square (X2) test. NS: Non-Significant; S: Significant; 2D: Two Dimensional; RR: Relative Risk; CI: Confidence Interval

Table 4: 2D gray-scale parameters in women who required emergency hysterectomy to stop bleeding compared with women who did not require hysterectomy.

of uterine serosa-bladder interface and 13.4 times (95% CI; 0.8-22.1) with Exophytic mass invading bladder by 2D gray scale ultrasound scan. (Table 3)

Regression analysis also showed that; the risk of emergency hysterectomy to control bleeding in studied cases of MAP increased; 3.2 times (95% CI; 2-5.2) with irregular retro-placental sonolucent areas, 4.5 times (95% CI; 2.2-9.4) with disruption of uterine serosa-bladder interface and 7.1 times (95% CI; 1.4-33.7) with Exophytic mass invading bladder by 2D gray scale ultrasound scan. (Table 4)

Best 2D gray-scale ultrasound parameters for detection of difficult placental separation and considerable intraoperative blood loss in studied cases were; abnormal placental lacunae (73.9% sensitivity) and exophytic mass invading bladder (100% specificity & 100% PPV). (Table 5)

Best 2D gray-scale ultrasound parameters for detection of emergency hysterectomy were; disruption of uterine serosa-bladder interface (81.8% sensitivity) and exophytic mass invading bladder (94.9% specificity, 66.7% PPV and 84.1% NPV). (Table 5)

DISCUSSION

Hemorrhagic and surgical complications associated of MAP depend on depth of placental invasion and involvement of adjacent structures.[21] MAP with bladder invasion is a serious, which necessitate proper antenatal diagnosis and appropriate management strategy.[22] Previous cesarean delivery and increased parity are the two known risk factors to MAP and incidence of MAP is increased concomitantly with increased cesarean section rates.[3,23-25]

Antenatal diagnosis of MAP is crucial for; proper counseling for possible surgical complications, multidisciplinary team care and recruitment.[3] Despite its cost and unavailability in many centers, MRI should be reserved for cases with inconclusive sonographic findings.[13,15,17]

Fifty pregnant women ≥28 weeks` gestation with expected MAP were studied (only 28 had MAP). 2D trans-abdominal gray-scale ultrasound scan done for studied women to confirm; placental location and findings suggestive of MAP. Intra-operative findings and histopathology results of removed uteri compared with pre-operative sonographer findings to detect accuracy of 2D gray-scale ultrasound scans in prenatal diagnosis of MAP. Forty-six of studied women were delivered at 35 weeks by planned cesarean section, while, 4 women were delivered at 33 weeks because of ante-partum hemorrhage. 56%(28/50) of studied women had difficult placental separation, considerable intraoperative blood loss and received intraoperative blood transfusion. In this study; parity, number of previous cesarean sections were significantly high among women, who had difficult placental delivery, women who had considerable intraoperative blood loss and women who required emergency hysterectomy to control bleeding. Wright et al found that; 41.7% of women with a known placenta accreta had a blood loss of ≥ 5000 (ml).[26]

Although, Wright et al, concluded that there was no

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-114

Variables	Sensitivity	Specificity	PPV	NPV
Accuracy of 2D gray-scale parameters in prediction of difficult placental separation, considerable intraoperative blood loss				
Loss of retro-placental sonolucent space	70%	59.3%	64.%	74.2%
Irregular retro-placental sonolucent area	72.6%	63%	65.5%	71%
Disruption of uterine serosa-bladder interface	43.5%	88.9%	76.9%	64.9%
Exophytic mass invading bladder	26.1%	100%	100%	61.4%
Abnormal placental lacunae	73.9%	37%	50%	62.5%
Accuracy of 2D Gray-Scale ultrasound parameters in prediction of emergency hysterectomy				
Loss of retro-placental sonolucent space	70%	48.7%	35.5%	70%
Irregular retro-placental sonolucent area	70%	53.8%	37.9%	70%
Disruption of uterine serosa-bladder interface	81.8%	82.1%	56.3%	84.1%
Exophytic mass invading bladder	63.4%	94.9%	66.7%	84.1%
Abnormal placental lacunae	72.7%	33.3%	23.5%	81.3%

Data represented as percentage. PPV: Positive Predictive Value; NPV: Negative Predictive Value. 2D: Two-Dimensional.

Table 5: Accuracy of 2D gray-scale ultrasound parameters in prediction of difficult placental separation, considerable intraoperative blood loss and emergency hysterectomy.

significant relation between parity, number of previous cesarean deliveries, degree of placental invasion and massive blood loss, Tikkanen, et al. found that; the risk factors of placenta accreta include parity, cesarean section and placenta previa.[26,27]

Also, Guleria, et al. concluded that; risk factors of AIP (abnormal invasive placentation) were placenta previa and previous cesarean delivery, and Thia, et al. concluded that depth of invasion in MAP is increased with multiple previous surgery or excessive curettage or infection causing defective decidua basalis.[28,29]

D'Antonio, et al. concluded that; incidence of AIP increased in past decades due to increasing caesarean section rates and ultrasound has 91% sensitivity and 97% specificity for prediction of all forms of AIP.[16]

Bilateral internal iliac artery ligation needed in 28%(14/50) of studied women, intrauterine compression balloon with placenta bed sutures needed in 6%(3/50) women and cesarean hysterectomy done in 22%(11/50) women. Histopathological examination of surgically removed uteri showed; placenta accreta in 10%(5/50) cases, increta in 8%(4/50) cases and percreta in 4%(2/50) cases. 10%(5/50) cases of bladder injury recorded during this study. Warshak et al, reviewed 99 women with pathologically confirmed placenta accreta.[30] Warshak, et al. concluded that; antenatal detection of placenta accreta was associated with significant decrease in maternal hemorrhage, also Tikkanen, et al. concluded that; antenatal diagnosis of placenta accreta may significantly reduce peripartum blood loss and Chantraine et al, concluded that; antenatal diagnosis of AIP reduces morbidity and undiagnosed cases of AIP led to more emergency hysterectomies.[27,30,31]

Eller, et al. concluded that; planned cesarean hysterectomy and pre-operative ureteric stents were associated with reduced maternal morbidity in MAP.[32]

In this study; best 2D gray-scale ultrasound parameters for detection of difficult placental separation and considerable intra-operative blood loss were; abnormal placental lacunae (73.9% sensitivity), exophytic mass invading bladder (100% specificity & 100% PPV) and loss of retro-placental sonolucent zone (74.2% NPV). Also, best 2D gray-scale ultrasound parameters for detection of emergency hysterectomy in studied cases were; disruption of hyperechoic uterine serosa-bladder interface (81.8% sensitivity) and exophytic mass invading bladder (94.9% specificity, 66.7% PPV and 84.1% NPV).

Dwyer, et al. studied 32 women to compare accuracy of trans-abdominal ultrasound and MRI for diagnosis of placenta accrete. They found that ultrasound identified placenta accreta with 93% sensitivity and ruled out placenta accreta with 71% specificity, while, MRI correctly identified placenta accreta with 80% sensitivity and ruled out placenta accreta with 65% specificity.[15]

Warshak, et al. found that ultrasound accurately diagnosed MAP with 77% sensitivity and ruled out MAP with 96% specificity, and, concluded that MRI may be helpful in diagnosis of MAP in cases with equivocal or inconclusive ultrasound findings.[13]

See comment in PubMed Commons bel Comstock and colleagues, to detect accuracy of ultrasound in detection of placenta accreta in high-risk patients, conducted large prospective study.[33] They, concluded that; multiple vascular spaces inside placenta (placental lacunae) was the most diagnostic sign for placenta accrete with high PPV and obliteration of retro-placental is not reliable sign for diagnosis of placenta accreta. Comstock and colleagues, found that absence of retro-placental space is not diagnostic sign to MAP, since the spaces may be normally absent without MAP and they recommended use of color Doppler to identify placental sinuses crossing the uterine wall to bladder.[33]

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-114

Wong, et al. concluded that loss of placental-uterine interface and prescence of abnormal vessels crossing this interface were the most specific criteria to diagnose the MAP using 2D gray-ultrasound scan.

Wong, et al. found that the major risk of placenta accreta is severe hemorrhage when the placenta separated at delivery. They concluded that the extent of myometrial involvement and the vascularity could assessed by the observation of the extent of placental – uterine wall interface disruption and the vessels crossing the interface disruption sites. In addition, they concluded that such assessment results in strategic planning of management of the placenta at delivery with favourable pregnancy outcomes.[34]

Japaraj, et al. found that the prominent gray scale ultrasound sign to diagnose the placenta accreta was dilated vessels extending from placenta to myometrium, also, Shi et al found that; the most prominent gray scale sign to diagnose the placenta accreta was dilated vessels extending from placenta to myometrium.[35,36]

CONCLUSION

Antenatal diagnosis of MAP is crucial for; proper counseling for possible surgical complications, multidisciplinary team care and recruitment. Best 2D gray-scale ultrasound parameters for detection of difficult placental separation in studied cases were; exophytic mass invading bladder, while, best 2D gray-scale ultrasound parameters for detection of emergency hysterectomy were; disruption of uterine serosa-bladder interface and exophytic mass invading bladder.

ACKNOWLEDGMENT

Authors are grateful to all women agreed to participate in this study.

CONFLICTS OF INTEREST

No conflict of interest exists in relation to this manuscript.

DISCLOSURE

All authors were contributed significantly and are responsible for the content of this manuscript.

REFERENCES

1. ACOG Committee Opinion. Placenta accreta. No. 266. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2002; 99: 169-170.

2. Abuhamad A. Morbidly adherent placenta. *Seminars in Perinatology.* 2014; 37(5): 359-364.

3. Usta IM, Hobeika EM, AbuMusa AA, Gabriel GE, Nassar AH. Placenta previa-accreta: risk factors and complications. *Am J Obstet Gynecol.* 2005; 193: 1045-1049. doi: 10.1016/j.ajog.2005.06.037

4. Silver RM. The MFMU cesarean section registry: maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol.* 2006; 107: 1226-1232.

5. Wortman AC, Alexander JM. Placenta accreta, increta, and percreta. *Obstet Gynecol Clin North Am.* 2013; 40(1): 137-154. doi: 10.1016/j.ogc.2012.12.002

6. Rao KP, Belogolovkin V, Yankowitz J, Spinnato JA 2nd. Abnormal placentation: evidence-based diagnosis and management of placenta previa, placenta accreta and vasa previa. *Obstet Gynecol Surv.* 2012; 67(8): 503-519. doi: 10.1097/OGX.0b013e3182685870

7. Khong TY. The pathology of placenta accreta, a worldwide epidemic. *J Clin Pathol.* 2008; 61: 1243-1246. doi: 10.1136/jcp.2008.055202

8. Gielchinsky Y, Rojansky N, Fasouliotis SJ, Ezra Y. Placenta accreta: summary of 10 years: a survey of 310 cases. *Placenta.* 2002; 23: 210-214. doi: 10.1053/plac.2001.0764

9. Getahun D, Oyelese Y, Salihu HM, Ananth CV. Previous cesarean delivery and risks of placenta previa and placental abruption. *Obstet Gynecol.* 2006; 107: 771-778.

10. Oyelese Y, Smulian JC. Placenta previa, placenta accreta, and vasa previa. *Obstet Gynecol.* 2006; 107(4): 927-941.

11. Eshkoli T, Weintraub AY, Sergienko R, Sheiner E. Placenta accreta: risk factors, perinatal outcomes and consequences for subsequent births. *Am J Obstet Gynecol.* 2013; 208(3): 219.e1-7. doi: 10.1016/j.ajog.2012.12.037

12. Chou MM, Ho ESC, Lee YH. Prenatal diagnosis of placenta previa accreta by transabdominal color Doppler ultrasound. *Ultrasound Obstet Gynecol.* 2000; 15: 28-35. doi: 10.1046/j.1469-0705.2000.00018.x

13. Warshak CR, Eskander R, Hull AD, et al. Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of placenta accreta. *Obstet Gynecol.* 2006; 108: 573-581. doi: 10.1097/01.AOG.0000233155.62906.6d

14. Zhang L, Li P, He GL, et al. Value of prenatal diagnosis of placenta previa with placenta increta by trans-abdominal color Doppler ultrasound. *Zhonghua Fu Chan Ke Za Zhi.* 2006; 41: 799-802.

15. Dwyer BK, Belogolovkin V, Tran L, et al. Prenatal diagnosis

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-114

of placenta accreta: sonography or magnetic resonance imaging? *J Ultrasound Med.* 2008; 27: 1275-1281.

16. D'Antonio F, Bhide A. Ultrasound in placental disorders. *Best Pract Res Clin Obstet Gynaecol.* 2014; 28(3): 429-442. doi: 10.1016/j.bpobgyn.2014.01.001

17. Moodley J, Ngambu NF, Corr P. Imaging techniques to identify morbidly adherent placenta praevia: a prospective study. *J Obstet Gynaecol.* 2004; 24(7): 742-744. doi: 10.1080/01443610400009402

18. Comstock CH, Lee W, Vettraino IM, Bronsteen RA. The early sonographic appearance of placenta accreta. *J Ultrasound Med.* 2003; 22: 19-23.

19. Al-Zirqi I, Stray-Pedersen B, Forsén L, Daltveit AK, Vangen S, NUR group. Validation study of uterine rupture registration in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand.* 2013; 92(9): 1086-1093. doi: 10.1111/aogs.12148

20. Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. *Am J Obstet Gynecol.* 2008; 199(5): 519.e1-7. doi: 10.1016/j.ajog.2008.04.049

21. Chou M, Chen WH, Tseng JJ, Chen YF, Yeh TT, Ho ESC. Prenatal detection of bladder wall involvement in invasive placentation with sequential two- Dimensional and adjunctive three-Dimensional Ultrasonography Taiwan. *J Obstet Gynecol.* 2009; 48(1): 38-45. doi: 10.1016/S1028-4559(09)60033-4

22. Comstock CH. Antenatal diagnosis of placenta accrete: a review. *Ultrasound Obstet Gynecol.* 2005; 26:89-96. doi: 10.1002/uog.1926

23. Bencaiova G, Burkhardt T, Beinder E. Abnormal placental invasion experience at 1 center. *J Reprod Med.* 2007; 52(8): 709-714.

24. Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol.* 2006; 107: 1226-1232. doi: 10.1097/01.AOG.0000219750.79480.84

25. Grobman WA, Gersnoviez R, Landon MB, et al. Pregnancy outcomes for women with placenta previa in relation to the number of prior cesarean deliveries. *Obstet Gynecol.* 2007; 110: 1249-1255 doi: 10.1097/01.AOG.0000292082.80566.cd

26. Wright JD, Pri-Paz S, Herzog TJ, et al. Predictors of massive blood loss in women with placenta accreta. *Am J Obstet Gynecol.* 2011; 205 (1): 38.e1-6. doi: 10.1016/j.ajog.2011.01.040

27. Tikkanen M, Paavonen J, Loukovaara M, Stefanovic V. Antenatal diagnosis of placenta accreta leads to reduced blood loss. *Acta Obstet Gynecol Scand.* 2011; 90(10): 1140-1146. doi: 10.1111/j.1600-0412.2011.01147.x

28. Guleria K, Gupta B, Agarwal S, Suneja A, Vaid N, Jain S. Abnormally invasive placenta: changing trends in diagnosis and management. *Acta Obstet Gynecol Scand.* 2013; 92(4): 461-464. doi: 10.1111/aogs.12083

29. Thia EW, Lee SL, Tan HK, Tan LK. Ultrasonographical features of morbidly-adherent placentas. *Singapore Med J.* 2007; 48(9): 799-802.

30. Warshak CR, Ramos GA, Eskander R, et al. Effect of predelivery diagnosis in 99 consecutive cases of placenta accreta. *Obstet Gynecol.* 2010; 115(1): 65-69. doi: 10.1097/AOG.0b013e3181c4f12a

31. Chantraine F, Braun T, Gonser M, Henrich W, Tutschek B. Prenatal diagnosis of abnormally invasive placenta reduces maternal peripartum hemorrhage and morbidity. *Acta Obstet Gynecol Scand.* 2013; 92(4): 439-444. doi: 10.1111/aogs.12081

32. Eller AG, Porter TF, Soisson P, Silver RM. Optimal management strategies for placenta accreta. *BJOG.* 2009; 116(5): 648-654. doi: 10.1111/j.1471-0528.2008.02037.x

33. Comstock CH, Love JJ Jr., Bronsteen RA, et al. sonographic detection of placenta accreta in the second and third trimesters of pregnancy. *Am J Obstet Gynecol.* 2004; 190: 1135-1140. doi: 10.1016/j.ajog.2003.11.024

34. Wong HS, Zuccollo J, Tait J, Pringle K. Antenatal topographical assessment of placenta accreta with Ultrasound Australian and New Zealand. *Journal of Obstetrics and Gynaecology.* 2008; 48: 421-443. doi: 10.1111/j.1479-828X.2008.00891.x

35. Japaraj RP, Mimin TS, Mukudan K. Antenatal diagnosis of placenta previa accreta in patients with previous cesarean scar. *J Obstet Gynaecol Res.* 2007; 33(4): 431-437. doi: 10.1111/j.1447-0756.2007.00549.x

36. Shi H, Pi P, Ding Y. Diagnosis of placenta previa accreta by two dimensional ultrasonography and color doppler in patients with cesarean section. *Zhong Nan Da Xue Xue Bao Yi Xue Ban.* 2012; 37(9): 939-943.

GYNECOLOGY AND OBSTETRICS RESEARCH

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ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-115

Research

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Volume 2 : Issue 3
Article Ref. #: 1000GOROJ2115

Article History:
Received: July 15th, 2015
Accepted: July 29th, 2015
Published: July 30th, 2015

Citation:
Juneau P. Analyzing pregnancy costs with finite mixture models: an opportunity to more adequately accommodate the presence of patient data heterogeneity. *Gynecol Obstet Res Open J*. 2015; 2(3): 69-76

Analyzing Pregnancy Costs with Finite Mixture Models: An Opportunity to More Adequately Accommodate the Presence of Patient Data Heterogeneity

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ABSTRACT

The choice of a model in the analysis of patient health care costs and utilization is critical for a clear understanding of the behavior and estimation of quantities like incremental costs or cost-effectiveness. In studying heath care claims related to pregnancy, it would not be surprising that a small portion of the women have costs associated with their care and treatment that might be extreme or outlying. Many strategies exist for accommodating outliers; however, is one approach superior to the others because it may be implemented over a broader set of conditions without making unreasonable assumptions about the prevailing data characteristics? In this study, the author will show an example of a data set based on the medical claims for over 300K pregnant women, aged 15-49, where the traditional, or widely used Generalized Linear Model (GLM) approach to modeling costs may be less than optimal due to the presence of patients with very large, or very small expenditure values. These values, in some sense "contaminate" the typically employed GLM and cause it to violate its underlying requisite statistical assumptions.

Finite Mixture Models (FMMs) have been employed in other areas of clinical research to model health care utilization. The author will introduce FMMs as an alternative to the commonly used GLM model and show that in his example data set, the fit of the FMMs is superior for the modeling of maternity expenditures in the presence of extreme or outlying cost values.

KEYWORDS: Maternal health care expenditures; Statistical model; Generalized linear model; Gamma distribution; Log link; Outlier; Residual; Finite mixture model; Akaike Information Criteria.

ABBREVIATION: GLM: Generalized Linear Model; FMMs: Finite Mixture Models; AIC: Akaike Information Criterion.

INTRODUCTION

It has been said that "beauty is in the eye of the beholder", but, so too is an investigator's understanding of phenomena a function of the lens that he or she uses to look at data. The estimates, inferences and/or conclusions that one draws from data are highly related to the way that the data are analyzed, modeled and presented. If an analyst makes a particular assumption about the prevailing characteristics of a data set and these conditions are absent, it is to no one's surprise that the subsequent downstream estimates, inferences and conclusions are at best, imprecise; at worst, erroneous.

Which analysis or model one uses to study health care costs has been the subject of debate amongst expert analysts in health outcomes research and resulted in numerous recom-

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-115

mendations.[1-7] Regardless of the philosophical position that one decides to take with respect to the analysis and/or modeling of health care costs, a critical part of the endeavor is to study the adequacy of the underlying assumptions that serve as the basis for this activity.[8,9] Without such an examination, the results derived from the data can be open to criticism and skepticism.

It has been the experience of the author, after over 26 years as a data analyst in many diverse areas of biomedical research, that the data characteristics necessary for an analysis or model to perform correctly are not frequently studied, but often assumed to be true and in some sense "robust" against departures from said features in the sample or samples. Moreover, it is also the author's contention that the verification of the requisite assumptions for an analysis or modeling exercise are often not shared with the reviewers and readers of published medical research.

A common model used to study total health care costs over many disease indications is a generalized linear model (GLM), assuming that the log of the mean costs describes the set of predictors or covariates in a linear fashion and that a gamma probability model adequately describes the distribution pattern of the observed data: its central tendency, spread, shape, etc. The author has employed such a model under many circumstances after checking that its assumptions were appropriate. However, what happens if the accepted GLM does not adequately represent the behavior of the total health care costs under study? Do other approaches exist to accommodate these departures for the requisite underlying statistical theory?

One circumstance where the standard GLM model has the potential to perform less than optimally is in the presence of extreme cost values, whether it is skewing to the high end (right), to the low (left), or in both the upper and lower range of the data set (longer "tails"); i.e., in a range than would not be reasonably predicted by the model. Such a circumstance can occur in disease indications where complications and/or particular co-morbidity patterns have the potential to increase treatment cost and expand the cost range dramatically.[10-14] The medical and pharmacy claims for women who are experiencing their first pregnancy are one such example where complications related to pregnancy can produce claims with high costs that expand or skew the cost distribution to a degree not anticipated by the conventional model.

In the face of extreme or outlying values, an analyst has a number of practices that he or she may engage in to reduce their influence or leverage on the chosen model. One approach is to analyze the data with the extreme values in and out of a model as a form of "sensitivity" analysis to see how the results vary by using these values and then removing them from the analysis. If the outlying values greatly influence the modeling results, it is common for analysts to examine the data for "assignable cause" (i.e., Are these extreme costs related to patients with unusual clinical characteristics that set them apart from most of the other patients?), subject the extreme values to some form of outlier test[15] or compare them with a known reference range.[16] Any one of these approaches can result in a loss of sample size because the investigators may decide to discard these patients from consideration after judging their costs relative to a frame of reference related to clinical experience ("assignable cause"), a cutoff point in a statistical test (outlier test) or a reference range gleaned from the related medical literature. This decreased sample size can then have downstream effects on the operating characteristics of statistical significance tests. Also, the outlying cases may have an important place in the context of the investigation, scientifically.[17,18]

Another approach to managing the outlying or extreme values involves the use of robust statistical methods to "downweight" their influence.[19] These methods are useful if extreme values exist in both the lower and upper ranges of the cost distribution. However, techniques like the application of a Winsorized or trimmed mean to remove outliers lose their statistical optimality[20] (e.g., unbiasedness) when a distribution is asymmetrical, which is often the case for cost data.[21-23]

An approach that may be employed, whether data are in the upper, lower, or both extreme ends of the cost range, and without having to resort to the removal of patient data from a sample is the application of a *finite mixture model*. A finite mixture model (FMM) consists of two or more underlying assumed distributions, such that each contributes to the understanding of overall data pattern a specific proportion of the time, with the sum of the proportions totaling to 1 or 100%.[24,25] For the sake of simplicity, suppose that the cost distribution can be described by two different probability structures. Then the contribution of one is p% (e.g., say, 25%) and the other is (100-p)% (in this example, that would be [100-25]% =75%). If f represents the overall probability density function for the data, it could be described by:

$$f = 0.25f_1 + 0.75f_2, \qquad (1)$$

where f_1 and f_2 are referred to as "component" probability density functions.

To further help the reader develop an intuition for the concept, suppose that we have an FMM consisting of underlying component distributions that are bell-shaped, Gaussian or normal. Figure 1 shows an example of an FMM, where 25% is from a normal with mean = 2.5 and standard deviation = 5 and the remaining three-quarters is from a normal with mean = 0 and standard deviation = 1.

Figure 1 shows an example of a *homogeneous* mixture. It is homogeneous because the two component distributions are bell-shaped, Gaussian, or normal. It is also possible to have a *heterogeneous* mixture of two different underlying distributions. Figure 2 shows an example of a mixture of 50% normal and 50% gamma.

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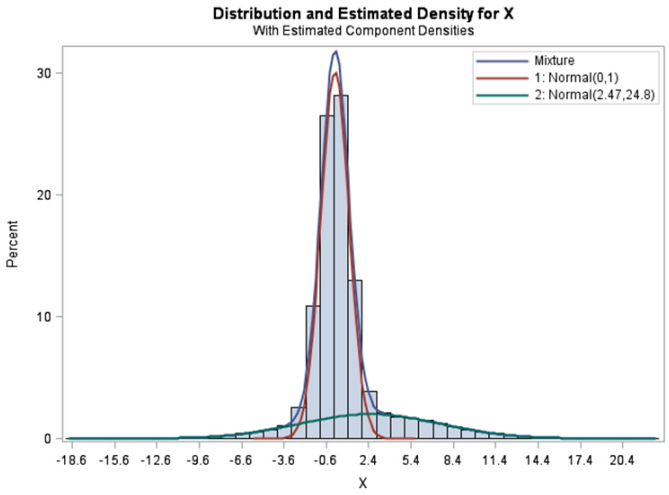

Figure 1: An example of a mixture of two normally distributed measurements.

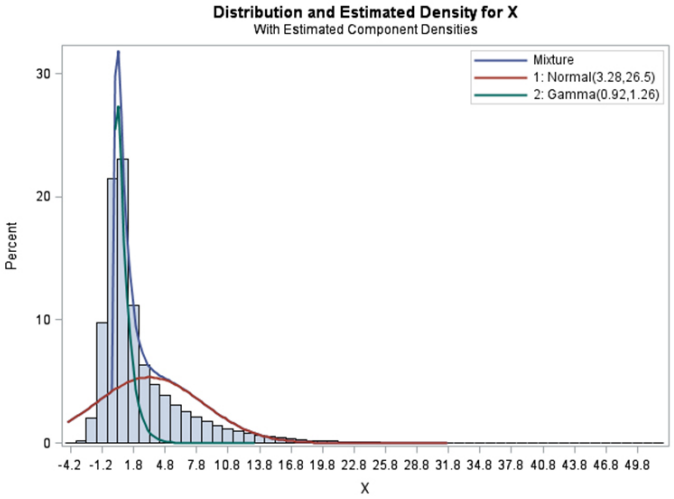

Figure 2: An example of a mixture of two measurements of different component distributions.

The FMM approach also allows an analyst to perform regression modeling; e.g., one could look at a mixture of cost values and see how well a set of co-morbidity or demographic characteristics predict the mean costs.

One the surface, FMM may seem like an interesting statistical or mathematical curiosity, but this approach to study cost data has been applied with success in various areas of clinical research.[26-29] Given that probability of a clinical complication during pregnancy is not zero, if one were to look at a large enough data set, he or she might end up with patients whose costs are on the order of millions of dollars. Certainly, such costs would exert influence on a regression model where most of the costs are within a lower anticipated range.

The advantage of the FMM approach is that the analyst does not really ever have to worry about whether a value is an outlier or not. If sufficient outliers exist, they may be modeled as part of a smaller, or minority component distribution in a cost model. The burden of examining the values for assignable cause is eliminated. Extreme data can occur at the high end, low end, or both in the cost range and studied with an FMM without the limitations imposed by robust statistical methods such as trimming.

The work in this paper is, to the knowledge of the author, the first application of an FMM to cost data in the setting of pregnancy. The author will share an example of a real data set that has properties that will demonstrate the benefits of the FMM approach when a portion of the costs are extremely low and high. These values effectively ruin the fit when standard cost models are employed.

DATA SOURCE

The data set for analysis consisted of 322,107 pregnant women aged 15-49 years using de-identified medical and pharmacy claims from the Truven Health MarketScan® Commercial Claims and Encounters database incurred between January 1, 2007 and December 31, 2011. The total health care costs were calculated from the date of the first pregnancy-related claim through to 3 months post-delivery, adjusted to 2011 dollars.

METHODS

The constructed data set was examined for its fidelity to a set of assumptions typically used in health care cost models that the costs could be adequately modeled with a gamma distribution.[30,31] First, the distribution of the costs was fit assuming a gamma distribution and compared with a kernel density estimate of the data distribution, an approach using more general assumptions and not imposing nor assuming a particular form for the cost data. A plot containing a histogram with the two superimposed distributions was used to make an initial assessment of the adequacy of the gamma assumption. Second, these data were fit with a small set of co-morbidity predictors and the model residuals were subject to an examination for the aptness of the gamma assumption a second time and for consideration of the appropriateness of the standard belief that the log of the mean costs could be related to the predictors in a linear fashion (i.e., that assuming a log link was plausible). After these two assessments, the data were refit using both heterogeneous and homogenous finite mixture models to compare their fit with the gamma assumption. The models with the lowest Akaike Information Criterion (AIC) were considered to be a better fit or description of the observed costs.

All data analysis, models and graphics were conducted using various SAS v 9.4 (TS1M2) procedures.

RESULTS

Figure 3 shows a histogram with two superimposed curves. One is a kernel density estimate of the distribution of the costs with minimal assumptions about its shape, scale, etc.

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The second curve was fitted assuming that the costs follow the standard assumption that they may be described by a gamma probability model. Figure 3a shows the data in its entirety. As the presence of patients with costs in the millions of dollars are part of the data set, the plot was run a second time with the data truncated at $100K. Figure 3b was only created for the sake of illustration purposes in this instance.

Figure 3b illustrates the main shortcoming of the choice of a gamma distribution for use as a cost model in this setting. The blue curve in Figure 3b is how an assumed gamma distribution would fit if it were used to describe the maternal cost data. Note that if an analyst were to use this model for these data the assumed distribution would over-predict how often the costs were on the lower and higher ends of the distribution and under-predict how often the costs would be around the mode, or most frequent value.

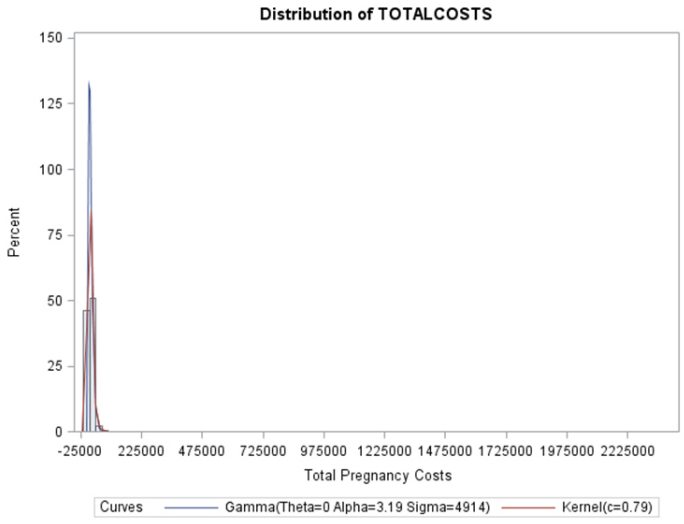

Figure 3a: A first look at the maternity total cost data.

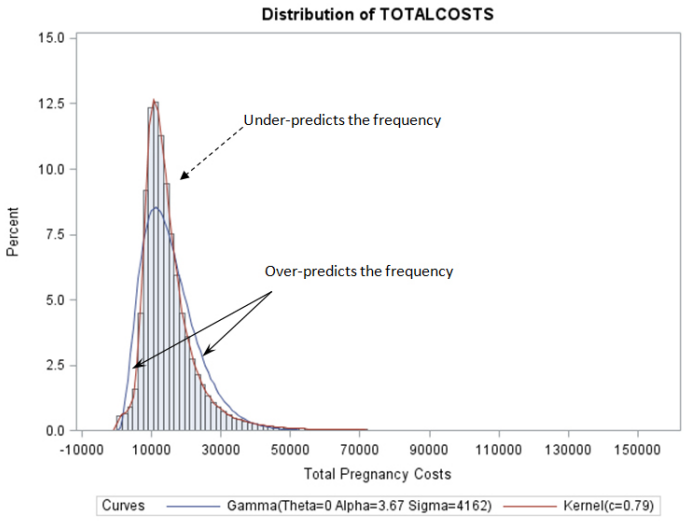

Figure 3b: A second look at the maternity total cost data – Truncated at $100K.

The initial plausibility of the appropriateness of the standard cost model is somewhat in doubt. The other feature of the standard model assumes that the predictors may be adequately described by a linear relationship with the log of the mean costs. In a GLM this assumed relationship is called the "link" between the mean costs and predictors. In Figure 4 the model was fit with a small set of 9 binary co-morbidity variables (presence v absence) and the assumption was checked by a special type of plot called a *cumulative residual plot*. Details regarding the statistics and construction of the plot may be found in other sources.[32,33] The main point of this plot is that the behavior of the actual data (dark blue solid curve – indicated by solid arrows) should fall within a set of bounds found (dashed, lighter blue region) by re-sampling the cost data several times. For the most part, the actual data do well and fall within the bounds, with the exception of the area in the purple-shaded boxes.

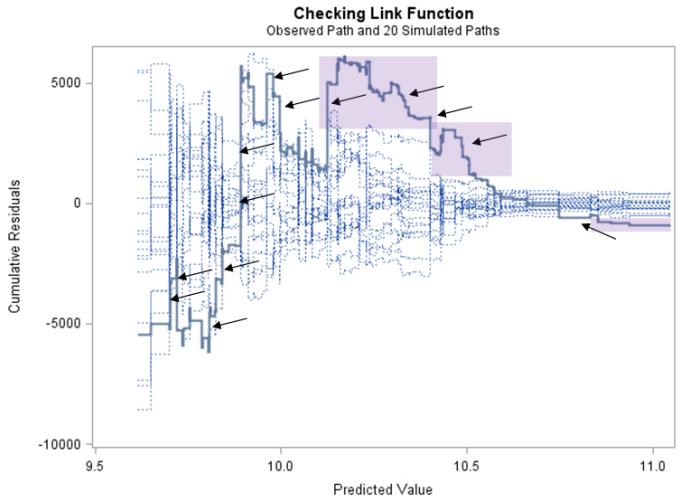

Figure 4: Cumulative residuals for a model assuming a log link.

Now, consider a simple approach to correct the shortcomings of the gamma and log link model. A standard regression technique is to try and look at the log of each patient's individual costs. A plot of the distribution of the log-transformed costs is shown in Figure 5.

In Figure 5 the log costs have been plotted and a superimposed kernel and normal curve were drawn over the data. The log transformed data that roughly follow a normal or bell curve are called *log normally distributed* data. This approach suffers from the similar problems to the gamma model; however, the pattern of over-estimation is reverse (for smaller values, the white area between the blue and red curves is larger on the left-hand side than was the case for the assumed gamma model in Figure 3b).

The short comings of these two models suggest that some heterogeneity exists in the cost data; *viz*., a single probability model or distribution will not adequately describe the behavior of the entire data set. Let's now attempt to fit an FMM to see if the description of such a model is superior to the ones

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previously employed.

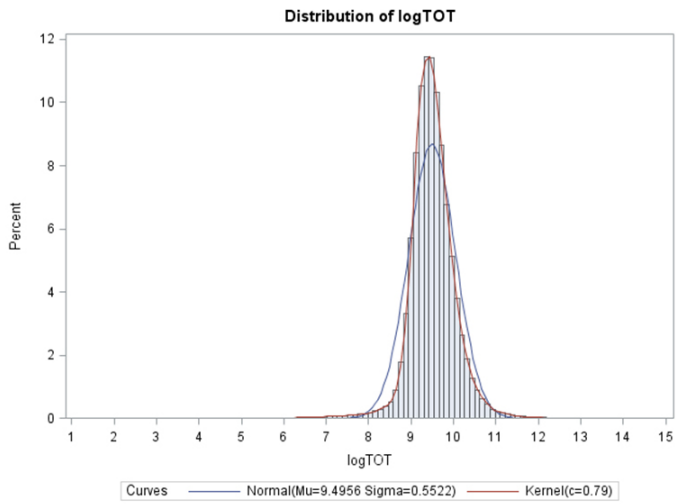

Figure 5: The distribution of the log-transformed costs.

Figure 6 consists of various FMM fit to the maternal cost data on the log scale. First attempts were with homogeneous FMMs. Recall that a homogeneous FMM consists of two or more probability models or distributions, but only differing in the values of their parameters, like the example in Figure 1 where both are bell-shaped curves, only differing in their means and standard deviations.

In Figure 6 the fitted model appears to be superior to that of the earlier single gamma or normal distributions (the latter fit on the log-transformed data). Using a SAS® procedure called PROC FMM, the results suggest that the first component (slightly larger mean, variance about 10x as larger) describes about 90% of the mixture, while another component describes the remaining 10%.

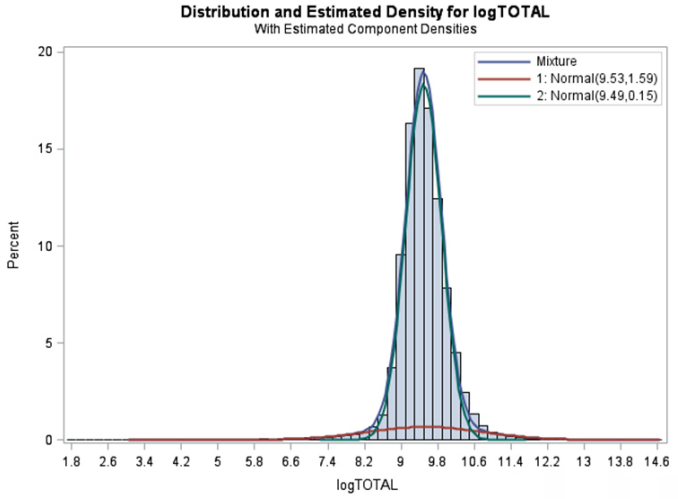

Figure 6: Homogeneous FMM fit to the maternal cost data using two normal distributions.

Figure 7 shows attempts to use various heterogeneous FMMs to describe the data. Only two component models were fit for this analysis.

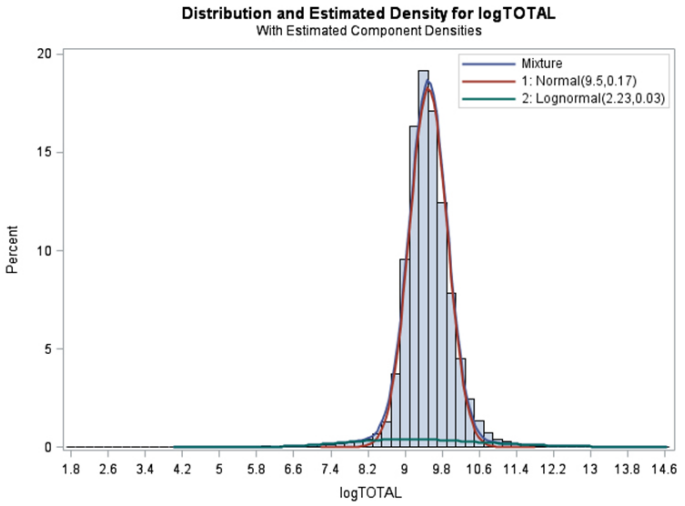

Figure 7a: A heterogeneous mixture of a normal and log-normal probability model.

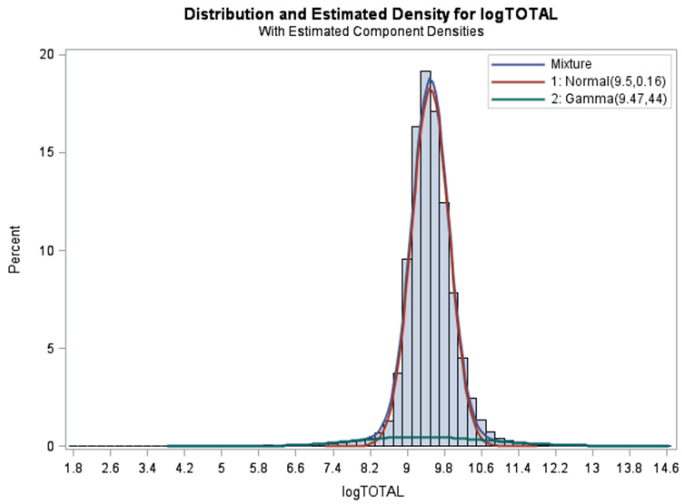

Figure 7c: A heterogeneous mixture of a normal and gamma probability model.

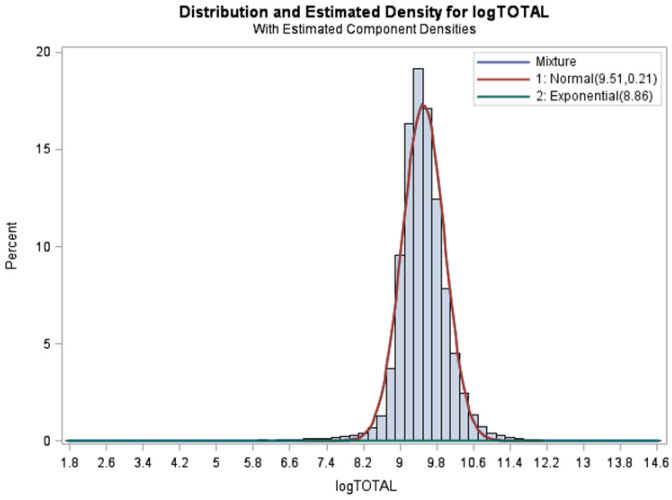

Figure 7b: A heterogeneous mixture of a normal and gamma probability model.

After examining Figures 6 and 7 it seems that all of these models are an improvement over the standard models, *visually*. Indeed, comparing one plot with another seems like an-

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-115

other "beauty contest" to find the best model. Fortunately, an analyst may use a statistic to differentiate between the models for a more objective choice.

The Akaike Information Criteria[34] (AIC) is a statistic that is often used to compare various models and their fit to data. Crudely, the AIC is a measure of the balance between underfitting a data set versus over-fitting by using too large of a number of parameters or a more complex model.[35,36] The AIC may be thought of as the sum of two quantities: the lack of fit for the model and a "penalty" for potential unreliability introduced by a more complicated model.[37] In a set of competing models, the model with the lowest AIC is considered to be the optimal one; in the context of FMM, AIC may be used to guide the selection of an optimal model.[38] Table 1 shows the AIC values for some models considered for the fit of the maternal cost data.

By virtue of the AIC values, the homogeneous FMM based on the log costs assuming two underlying normal probability models would seem like the best model to describe the maternal costs.

DISCUSSION

Modeling a phenomenon involves the process of reducing it down to a set of features by detail abstraction and assuming that underlying conditions persist. Thus, for cost data, the analyst assumes a probability model that, in itself, describes the behavior of the cost data distribution and presumes that it has a specific shape, scale, or other characteristics that may be readily identifiable, mathematically (i.e., may be specified by a formula). When an analyst picks a model without checking its adequacy, he or she is imposing features on the data or "viewing it through a lens" that might distort reality because of assumptions that cannot be supported upon closer examination of the data. All estimates and inferences derived under these faulty or unchecked assumptions can be imprecise, or in error, respectively. For medical indications where a great deal of underlying heterogeneity exists, FMMs have been shown to more adequately describe the data characteristics and reflect the reality of the cost data than standard models. The author contends that their application in the study of costs related to pregnancy may be another area where the FMM approach more adequately describes the data, especially if specific medical complications exist and occur infrequently, but often enough to undermine the appropriate use of a more traditional, single distribution or probability model. His study is a first case analysis of the potential for FMMs in modeling of costs in gynecology and obstetrics.

In an age when increasing health care costs are falling under greater scrutiny by payers, a sensible starting place for greater understanding is to check the way that data are used to make estimates of incremental costs or cost-effectiveness. Are the results derived from a model based on a defensible or rational approach that is faithful to the features of the data? Are the prevailing conditions observed in the clinical environment addressed in the model? Equipped with the appropriate tools, the analyst is allowed to share a more accurate vision of the behavior of costs associated with pregnancy, which may lead to a more precise estimates of incremental costs or cost-effectiveness, and ultimately, serve the best interests for the treatment and care of pregnant women.

ACKNOWLEDGEMENTS

Financial support for this research was provided by Bayer Healthcare Research and Truven Health Analytics.

CONFIDENTIALITY/CONSENT STATEMENT

The data used for this study did not involve the interaction or interview with any subjects and the data does not include any individually identifiable data (e.g. does not include names, addresses, social security or medical record numbers or other obvious identifiers) and as such is not research involving human subject as defined at 45 CFR 46.102(f)(2). Furthermore, this study used existing fully de-identified and the investigator(s) cannot be identified, directly or through identifiers linked to subjects

Model	Model Type	AIC
Gamma on Untransformed Costs	Traditional Single Probability Model	6690934
Normal on Log-Transformed Costs	Traditional Single Probability Model	531525
10% Normal(mean=9.53, variance=1.59) + 90% Normal(mean=0.15, variance =0.15) on Log-Transformed Costs	Homogeneous FMM	459427
92% Normal(mean=9.50, variance=0.16) + 8% Gamma(intercept=2.25, scale= 44.04) on Log-Transformed Costs	Heterogeneous FMM	461699
98% Normal(mean=9.51, variance=0.21) + 2% Exponential(intercept=2.18) on Log-Transformed Costs	Heterogeneous FMM	484566
26% Normal(mean=9.9, variance=0.35) + 74% Weibull(intercept=2.26, scale=0.04) on Log-Transformed Costs	Heterogeneous FMM	481570

Table 1: AIC values comparing single, homogeneous and heterogeneous FMMs.

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-115

and as such is exempt from 45 CFR 46.101(b)(4) from all 45 CFR part 46 requirements. Consequently, IRB approval is not required.

REFERENCES

1. Diehr P, Yanez D, Ash A, Hornbrook M, and Lin DY. Methods for analyzing health care utilization and costs. *Annual Rev Pub Health*. 1999; 20: 125-144. doi: 10.1146/annurev.publhealth.20.1.125

2. Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. *Health Services and Outcomes Res Method*. 2000; 1(2):185-202. doi: 10.1023/A:1012597123667

3. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? *J Health Econ*. 2001; 20: 461-494. doi: 10.1016/S0167-6296(01)00086-8

4. Buntin MB, Zaslavsky AM. Too much ado about two-part models and transformation? comparing methods of modeling medicare expenditures. *J Health Econ*. 2004; 23: 525-542. doi: 10.1016/j.jhealeco.2003.10.005

5. Montez-Rath M, Christiansen CL, Ettner SL, Loveland S, Rosen AK. Performance of statistical models to predict mental health and substance abuse costs. *BMC Medical Res Method*. 2006; 6: 53 doi: 10.1186/1471-2288-6-53

6. Mullahy M. Econometric modeling of health care costs and expenditures: a survey of analytical issues and related policy considerations. *Med Care*. 2009; 47(7): S104-S108. doi: 10.1097/MLR.0b013e31819c9593

7. Mihaylova M, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare costs and resources. *Health Econ*. 2010; 20(8): 897-916. doi: 10.1002/hec.1653

8. McCullagh P, Nelder, JA. Generalized linear models, 2/e. New York, NY USA: Chapman & Hall; 1991.

9. Myers RH, Montgomery DC, Vining GC. Generalized linear models in engineering and the sciences. New York, NY USA: John Wiley & Sons, Inc.; 2002.

10. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Critical Care*. 2004; 8(5): R291-R298 doi: 10.1186/cc2893

11. Carls GS, Lee DW, Ozimnkowski RJ, Wang S, Gibson TB, Stewart E. What are the total costs of surgical treatment for uterine fibroids? *J Women's Health*. 2008; 17(7): 1119-1132. doi: 10.1089/jwh.2008.0456

12. Brem H, Maggi J, Nierman D, et al. High cost of stage IV pressure ulcers. *Am J Surg*. 2012; 200(4): 473-477. doi: 10.1016/j.amjsurg.2009.12.021

13. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual costs of uterine leiomyomata in the United States. *Am J Obset Gynecol*. 2012; 206(3): 211.e1-211.e9. doi: 10.1016/j.ajog.2011.12.002

14. Yeaw J, Halinan S, Hines D, et al. Direct medical costs for complications among children and adults with diabetes in the US commercial payer setting. *Appl Health Econ Health Policy*. 2014; 12(2): 219-230. doi: 10.1007/s40258-014-0086-9

15. Barnet V, Lewis T. Outliers in statistical data. New York, NY USA: John Wiley & Sons; 1979.

16. Harris EK, Boyd JC. Statistical bases of reference values in laboratory medicine. New York, NY USA: Marcel Dekker, Inc.; 1995.

17. Kandel R. Our changing climate. New York, NY USA: McGraw Hill; 1991.

18. Vitello P. Joseph Farman, 82 is dead; discovered ozone hole. New York Times. May 20, 2013: B9.

19. Maronna RA, Martin RD, Yohai VJ. Robust statistics: theory and methods. New York, NY USA: John Wiley & Sons; 2006.

20. Rivest L-P. Statistical properties of winsorized means for skewed distributions. *Biometrika*. 1994; 81(2): 373-383.

21. Dunn G, Mirandola M, Amaddeo F, Tansella M. Describing, explaining or predicting mental health care costs: a guide to regression models: methodological review. *British J Psych*. 2003; 183: 398-404. doi: 10.1192/bjp.183.5.398

22. Griswold M, Parmigiani G, Potsky R, Lipscomb J. Analyzing health care costs: a comparison of statistical methods motivated by medicare colorectal cancer charges. *Biostatistics*. 2004; 1(1): 1-23.

23. Başer O. Modeling transformed health care costs with unknown heteroskedasticity. *App Econ Res Bull*. 2007; 01: 1-6.

24. Kessler D, McDowell A. Introducing the FMM procedure for finite mixture models. https://support.sas.com/resources/papers/proceedings12/328-2012.pdf ; Accessed July 9, 2015.

25. McLachlan G, Peel D. Finite mixture models. New York, NY USA: John Wiley & Sons; 2000.

26. Deb P, Trivedi PK. Demand for medical care for the elderly: a finite mixture approach. *J Appl Econometrics*. 1997; 12: 313-336.

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-115

27. Deb P, Holmes AN. Estimates of use and cost of behavioral health care: a comparison of standard and finite mixture models. In: Jones A and O'Donnell O. ed. Econometric analysis of health data. Chichester, West Sussex, UK: John Wiley and Sons; 2002: 87-99.

28. Lourenço OD, Ferreira PL. Utilization of public health centres in Portugal: effect of time costs and other determinants. finite mixture models applied to truncated samples. *Health Econ*. 2005; 14: 939-953. doi: 10.1002/hec.1046

29. Rein DB. A matter of classes: stratifying health care populations to produce better estimates of inpatient costs. *Health Serv Res*. 2005; 40(4): 1217-1233. doi: 10.1111/j.1475-6773.2005.00393.x

30. Pierce DA, Schafer DW. Residuals in generalized linear models. *J Amer Stat Assoc*. 1986; 81(396): 977-986. doi: 10.2307/2289071

31. Dunteman GH. Introduction to generalized linear models. London, UK: Sage Publications; 2006.

32. Lin DY, Wei LJ, Ying Z. Model-checking techniques based on cumulative residuals. *Biometrics*. 2002; 58: 1-12. doi: 10.1111/j.0006-341X.2002.00001.x

33. The GENMOD procedure. SAS/STAT user's guide, 2/e. http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_genmod_sect060.htm; Accessed July 9, 2015.

34. Akaike H. Likelihood of a model and information criteria. *J Econometrics*. 1981; 16: 3-14.

35. Bozdogan H. Akaike's information criteria and recent developments in information complexity. *J Math Psychol*. 2000; 44: 62-91. doi:10.1006/jmps.1999.1277

36. Anderson DR, Burnham KP, White GC. Comparison of akaike information criteria and consistent akaike information criteria for model selection and statistical inference from capture-recapture studies. *J App Stat*. 1998; 25(2): 263-282. doi: 10.1080/02664769823250

37. Mutua FM. The use of akaike information criterion in the identification of an optimum flood frequency model. *Hydrological Sciences J*. 1994; 39(3): 235-244.

38. The FMM Procedure. SAS/STAT User's Guide. 13.2. http://support.sas.com/documentation/cdl/en/statug/67523/HTML/default/viewer.htm#statug_fmm_overview.htm . Accessed July 9, 2015.

GYNECOLOGY AND OBSTETRICS RESEARCH

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ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-116

Case Report

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Volume 2 : Issue 3
Article Ref. #: 1000GOROJ2116

Article History:
Received: August 6th, 2015
Accepted: August 17th, 2015
Published: August 18th, 2015

Citation:
Bacalbasa N, Balescu I, Lamasz A. Bilateral massive hematoma of bartholin glands after prolonged labour: a case report. *Gynecol Obstet Res Open J*. 2015; 2(3): 77-79.

Bilateral Massive Hematoma of Bartholin Glands after Prolonged Labour: A Case Report

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ABSTRACT

Background: The early postpartum hematoma represents a rare complication which can appear in the early post-partum period. Its formation and development is favoured by the hypervascularization of the genital area during pregnancy and by the cellular hormone-dependent laxity of the tissues which favours its apparition and diffusion.
Description of the case: We present a rare situation of a large bilateral Bartholin glands hematoma at a 27-years-old, primiparous female, who had experienced a prolonged labour, ended by a caesarean section.
Conclusion: Early postpartum hematoma is a rare condition which might need in selected cases a surgical approach in order to resect the compromised structures.

KEYWORDS: Delivery; Massive hematoma; Bartholin glands.

INTRODUCTION

Puerperal hematoma is a rare complication which might develop after delivery and which might put the mother's life in danger if not recognized in time.[1,2] Statistically, the incidence of puerperal hematoma widely varies between 1/300 and 1/1500 deliveries while the rate of cases necessitating surgical treatment is almost 1/900 cases.[3-6] Most often, puerperal hematomas develop in the peri-vaginal or peri-vulvar spaces, in the lax tissues, tending to widely dissect the spaces where no anatomical obstacle is present. At this level, due to the high levels of pregnancy hormones there is a limited possibility of spontaneous haemostasis; secondarily, the hematoma might dissect the peri-vaginal and peri-rectal spaces, ascending to the retroperitoneal space.[3] The most common localizations are the vaginal, vulvar and pelvic ones.[3] We present the case of a 27-year-old primiparous patient who developed a massive bilateral vulvar hematoma after a prolonged labour followed by a Ceasarian section, associated with perineal debilitating pain, fever and difficulties in defecation. The hematoma proved to be entirely developed into the Bartholin glands, which were irreversibly compromised. A total bilateral resection of Bartholin glands was performed.

CASE REPORT

A 27-year-old primiparous woman referred herself to Obstetrics clinic during the 39th week of gestation for sustained uterine contractions; the local examination revealed a quasi-complete cervical dilation; after a negative labour test the patient was submitted to a Caesarean section. Three days after surgery the patient reported the apparition of two tumoral, renitent lesions with vulvar localization, with mass effect on the distal vagina and anal canal. The clinical examination revealed that the anterior perineal region was significantly tumefied and very painful when touched (Figure 1). The vaginal examination revealed the presence of

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-116

two pseudotumoral lesions located on the lateral vaginal wall. The perineal MRI showed the presence of two heterogeneous, hyperintense in T1 hematomas measuring 6/5 cm on the right side and 4/3 cm on the left side of the outer lips (Figures 2 and 3). The patient was resubmitted to surgery, intra-operatively a bilateral massive hematoma of the Bartholin glands being found, with total destruction of the glandular structures. A total bilateral resection of Bartholin glands was performed (Figures 4, 5 and 6). The postoperative evolution was uneventful, the patient being discharged the 4th postoperative day.

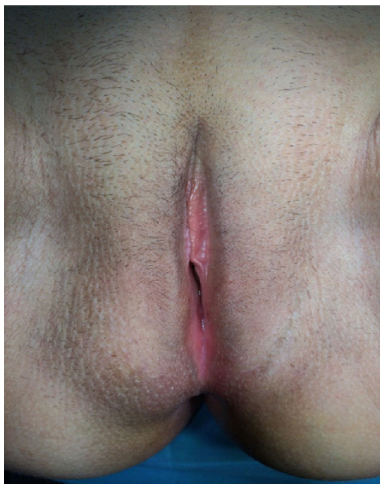

Figure 1: Bilateral tumefaction of the anterior perineal region.

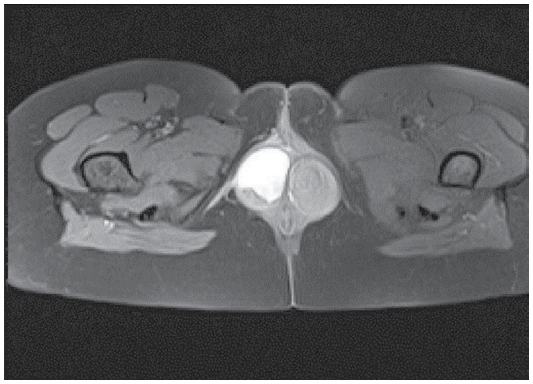

Figure 2: The MRI study revealed the presence of two heterogeneous, hyperintense in T1 hematomas.

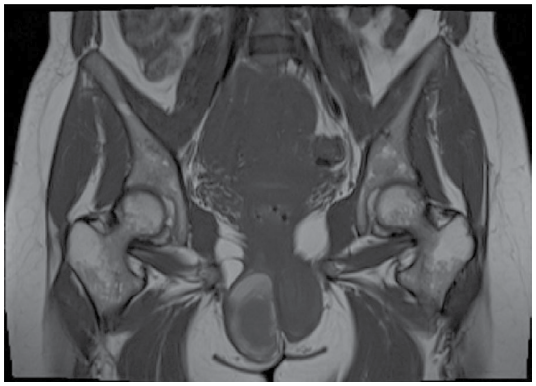

Figure 3: The two hematomas measuring 6/5 cm on the right side and 4/3 on the left side are located in the outer lips.

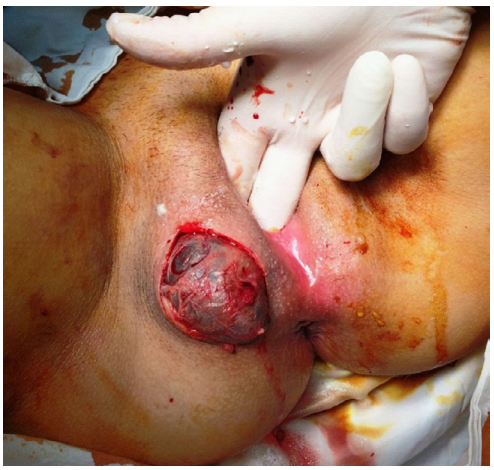

Figure 4: The Bartholin glands are completely compromised due to the large hematomas.

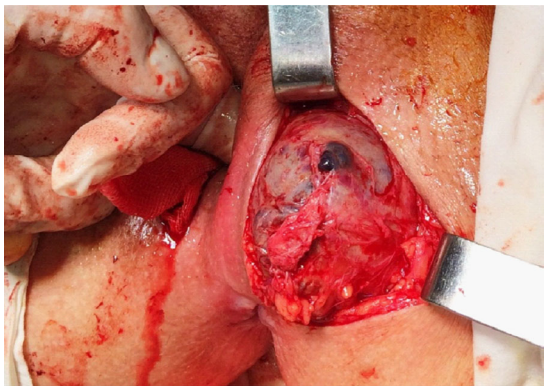

Figure 5: The Bartholin glands are completely compromised due to the large hematomas.

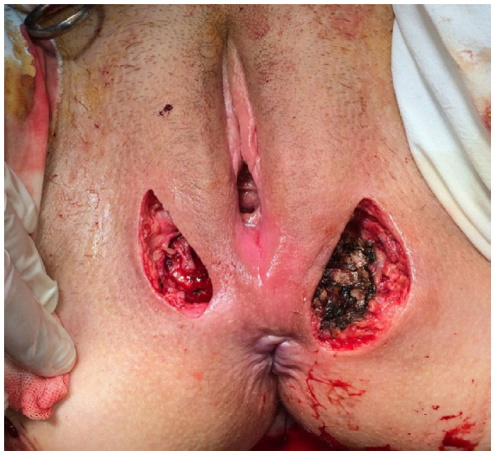

Figure 6: The final aspect after bilateral resection of Bartholin glands.

DISCUSSION

Most puerperal hematomas develop due to the lacerations which might appear during labour or due to the instrumental extractions, especially due to the use of forceps.[3] Primiparity represents a particular risk factor, which, in association with a prolonged labour, a foetal weight over 4000 gr, coagulation disorders or vulvovaginal varicosities significantly increase the risk

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-116

of developing puerperal hematomas.[3,7]

Unless the puerperal hematomas develop secondarily to peri-partum traumatisms such as episiotomy or vulvo-vaginal ruptures, they can be related to a secondary necrosis of the small calibre arteries which might be compressed by a too slow descend of the foetal head. Once the hematoma appears, it will have no spontaneous tendency to regress; contrarily it will develop a progressive growth and will compress the surrounding tissues. For this reason, the secondary vascular necrosis might affect blood vessels with increasing diameters.[3]

When it comes to the chronological classification of puerperal hematomas, they can be considered as early and late lesions.[8] In our case we can consider that the hematoma was an early one, developed immediately after the decompression of the perineal region by Caesarean section. In that moment, the small calibre vessels which had been already compressed by the foetal head and necrotised developed a bleeding at the level of the Bartholin glands which was recognized and diagnosed in the third postoperative day.

The second widely recognized classification is the anatomical one which divides the puerperal hematoma into vaginal, vulvar and subperitoneal. In fact, this classification is an essential one because it creates a net separation between vulvar and vaginal hematoma on one side and subperitoneal hematomas on the other side, the two groups having totally different therapeutic strategies.[3] The particularity of our case is the atypical localization, neither vulvar nor perineal but localized symmetrically at the level of the Bartholin glands.

When it comes to the most appropriate therapeutic strategy, it depends on location and dimension of the lesions. While for vaginal or vulvar hematoma a conservative treatment might be taken in consideration especially for the small sized lesions, subperitoneal and retroperitoneal hematomas usually benefit from surgical treatment, although a conservative therapy might be also taken in consideration.[9]

In our case, we decided to perform a surgical manoeuvre consisting of Bartholin glands resection due to the fact that their structure had been already destroyed by the ischemic modifications induced by the compressive hematoma.

To the best of our knowledge, no other case of bilateral Bartholin gland hematoma has been described.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

The patient has provided written permission for publication of the case details.

REFERENCES

1. Pinborg A, Bodker B, Hogdall C. Postpartum hematoma and vaginal packing with a blood pressure cuff. *Acta Obstet Gynecol Scand.* 2000; 79(10): 887-889. 10.1034/j.1600-0412.2000.079010887.x

2. Kehila M, Khedher SB, Zeghal D, Mahjoub S. Conservative management of postpartum hematomas large volume: about 3 cases. *Pan Afr Med J.* 2013; 16: 9. doi: 10.11604/pamj.2013.16.9.1918

3. Jacquetin B, Boulleret C, Fatton B. Thrombus genital, extract updates gynaecology and obstetric-tome. 1998.

4. Pieri RJ. Pelvic hematomas associated with pregnancy. *Obstet Gynecol.* 1958; 12(3): 249-258.

5. Villella J, Garry D, Levine G, Glanz S, Figueroa R, Maulik D. Postpartum angiographic embolization for vulvovaginal hematoma. A report of two cases. *J Reprod Med*. 2001; 46(1): 65-67.

6. Zahn CM, Yeomans ER. Postpartum hemorrhage: placenta accreta, uterine inversion, and puerperal hematomas. *Clin Obstet Gynecol.* 1990; 33(3): 422-431.

7. Ridgway LE. Puerperal emergency, Vaginal and vulvar hematomas. *Obstet Gynecol Clin North Am.* 1995; 22(2): 275-282.

8. Visscher HC, Visscher RD. Early and late postpartum hemorrhage. In: Sciarra RJ, ed. *Gynecology and Obstetrics*. Philadelphia: Harper & Row. 1987; 1-5.

9. Vanlieferinghen S, Piketty M, Blumental Y, Jouannic JM, Desfeux P, Benifla JL. Giant retroperitoneal hematoma in the peripartum of a normal delivery, expectative attitude. *Gynecol Obstet Fertil*. 2011; 39(3): e61-e63. doi: 10.1016/j.gyobfe.2011.01.002