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Violence Against Women: A Global Perspective

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Violence against women is rampant in all corners of the world and devastates the lives of millions of women. It is rooted in a global culture of discrimination which denies women equal rights with men, legitimizing the appropriation of women's bodies for individual gratification or political ends.[1] It feeds off discrimination and serves to reinforce it. This is compounded by discrimination on the grounds of race, ethnicity, sexual identity, social status, class, and age. Such forms of discrimination restrict women's choices, increase their vulnerability to violence and deprive them of justice.

The United Nations defines violence against women as, "any act of gender-based violence that results in, or is likely to result in, sexual or mental harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or in private life".[2 (p1)] Violence against women, particularly intimate partner violence and sexual violence are major public health problems and violations of women's human rights. Global estimates indicate that about 1 in 3 women worldwide have experienced either physical and/or sexual violence in their lifetime. Such violence can negatively impact a women's physical, mental, and reproductive health. It also affects their children, family, social and economic life. Some have fatal outcomes like homicide or suicide.

Violence against women can lead to physical health problems such as chronic headaches, back pain, fibromyalgia, GI disorders, limited mobility, abdominal pain, and overall poor health. It also leads to smoking, drug misuse and alcoholism. Impact on their mental health can include depression, post-traumatic stress disorder (PTSD), anxiety, insomnia, eating disorders, alcoholism, and suicide attempts. In addition, such violence during pregnancy increases the likelihood of an abortion, stillbirth, preterm births, sexually transmitted infections, and low weight newborns.[2]

Children who witness violence or grow up in families where they are exposed to violence may suffer from a range of behavioral and emotional disturbances. They too may become perpetrators later in their lives or be a victim of violence. Either way, they are negatively impacted for life.

The social and economic damage caused by violence against women are tremendous and have a ripple effect throughout the society. Many women, as a result of violence, may suffer isolation, face an inability and unwillingness to work or support themselves, loss of productivity in the workforce, lack participation in normal activities of life, and have a limited ability to care for themselves and their families.

There are numerous forms of violence against women, such as femicide (intentional murder of women), sexual assaults, female genital mutilation/cutting, human trafficking, sexual harassment, rape, forced child marriages, intimate partner violence, stalking, dating violence, and elder abuse.[3] Thirty years ago, most forms of violence against women were hidden under a cloak of silence or acceptance – No more! As more women came out with allegations of abuse and violence, it became apparent that violence occurred on a massive scale; that no woman is immune, and that family, friends, and public institutions had become insensitive to it. Since

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then, women have mobilized to offer direct services and shelter those who have encountered violence, to educate communities about the rage of violence against women, and to develop strategies for change.

People need to come out in large numbers to actively address and draw attention to this global disgrace. Activist movements happen in many forms and operate at local, national and international levels to bring about change. Until women become empowered and educated worldwide, their status will continue to remain low and they will always be mistreated. The international community needs to work together to enforce women's rights and equality.

Violence against women is a violation of human rights that cannot be justified by any political, religious, or cultural norm. It is not only a consequence of gender inequality, but reinforces women's low status in society and the multiple disparities between women and men. Violence against women emanates from their lack of control and power, as well as the social norms that prescribe men and women's roles in our society. A global culture of discrimination against women allows violence to occur daily and without punishment to the perpetrator. This narrative should evoke awareness and raise your conscious to this global injustice. Look deep inside yourself to help eradicate violence against women and endow them with lives of equality and human dignity!

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Research

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Perception of Fatigue in Female Nurses Employed in Hospitals

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ABSTRACT

Background: Fatigue is the inability to maintain the required stamina in work capacity with consequences affecting occupational performance, health, and safety. Women are often more exposed to the risk of fatigue because they tend to be multitaskers. The present survey is aimed at determining the perceived fatigue in female nurses employed in hospitals and identifying the individual and occupational factors affecting it.
Methods: This survey was conducted on 270 female nurses. The sample was selected using multistage randomized stratified multistage sampling. To collect the data, a demographic and occupational information, and Iowa Fatigue Scale (IFS) were filled using the self-report technique. The gleaned data were analyzed with SPSS16 using analysis of variance (ANOVA), T-test and, and Pearson correlation coefficient.
Results: The overall score of nurses fatigue was 30.78±7.90. There was a statistically significant difference between employment status (p=0.01), husband's support (p=0.00), age (p=0.008), and work experience (p=0.02) on one hand, and fatigue. There was no significant difference between marital status (p=0.23), type of ward (p=0.59), official position (p=0.51), work shift (p=0.29), having a suckling (p=0.10), having a second job (0.25), and monthly work hours (p=0.38) and fatigue.
Conclusion: Based on the findings of this survey, a moderate degree of fatigue was observed among female nurses employed in clinical wards. Also, factors such as age, being married, employment status, and husband's support have considerable impact on the perceived fatigue. This demands the application of preventive interventions to decrease fatigue in female nurses specifically for older married nurses with permanent employment.

KEYWORDS: Fatigue; Nurses; Women's health.

ABBREVIATIONS: IFS: Iowa Fatigue Scale; ANOVA: Analysis of variance; LSD: Least Significant Difference.

INTRODUCTION

Fatigue is described as a state of drowsiness which originates from the physiological mechanisms related to sleep and circadian rhythm affecting the individual's response to psychosomatic needs.[1] This state usually results from physical and spiritual disorders, stress, and overworks.[2] That is why fatigue is also defined as the inability to maintain and preserve the required or expected stamina and energy or the lack of energy in the working capacity.[3] Working with fatigue is even equated to alcoholism.[4]

The nursing profession is among those jobs in which the staff works in various work shifts.[5] Individuals who work in the night shift in circulating rounds are exposed to lack of sleep[6] which is associated with increasing fatigue.[5] This exerts detrimental effects on the nurses health,[7] linked to dysfunction in the physical and cognitive performance of persons.[8] The con-

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sequences of this dysfunction influence the individuals occupational and organizational performance, and affect their heath.[9] The consequences of fatigue include reduced memory, reduced reaction time, decreased speed of information processing, irritability, endangering of problem solving and critical thinking, slipping in paying attention to details, decreased concentration, judgment, and motivation.[4] Also, regarding the point that fatigue is associated with serious damage to the nursing staff including musclar-skeletal and cardiovascular damages, etc.,[9,10] on the whole, fatigue may lead to reduced output, dissatisfaction, absence from work, increased sick leave, and high turnover of the personnel[11-13] enhancing the decision for leaving the occupation.[5] All these affect the nursing planning and implementation of effective nursing interventions[14] leading to the emergence of treatment errors and resulting in negative health-care consequences. Since the nurses are in charge of the safety of their patients, factors such as long work hours and exhaustion are threatening the patients safety.[15]

Indeed, the shortage of nurses is a global problem and it is mandatory to pay special attention to the challenges and problems within their work environment that nurses face. In other words, issues related to work stress and psychologic factors such as weariness, depreciation, and burnout should be given prompt and sufficient attention. Besides, provision of psychological health in the work environment is an important strategy for keeping nurses interested and improving the nursing environment.[13] The working ability is a dynamic process which is constantly changing in the course of life. It is the result of interactions between manpower and work characteristics and can be maintained and even repaired *via* implementing the necessary interventions required for promoting health and prevention of fatigue.[11]

The present evidence does not provide any specific sources for fatigue in the work environment[9,10] as the concept of fatigue is a multi-factorial one.[13] Nonetheless, some hypothesis have been presented indicating the association between fatigue and circadian rhythm, quantity and quality of sleep, personal hygiene, work environment and duties, long work hours, insufficient rest, excessive stress, or a combination of these.[9,10] According to studies based on different populations, the prevalence of fatigue is about 10-45%, with women being 1.5 times more at the risk of fatigue[15] and prevalence of compassion fatigue in nursing is 7.3% and 40%.[16] The number of female personnel in health professions is more than men. On the other hand, in addition to occupational responsibilities, women handle other duties such as childbirth, raising children, and managing the home environments which demand sustaining more stressful situations. This reminds us of the increased risk in women and demands more attention to the phenomenon of fatigue in them.[17,18] On the other hand, medical errors and employee injuries are serious challenges in the healthcare system. Fatigue in nursing has been linked to both of these factors.[19] However, their own reactions have not been systematically addressed.[20] Furthermore, stresses may vary across healthcare work environments resulting in varying levels of fatigue across contexts, and little emphasis has been placed on the potential health consequences for nurses providing care.[21]

Finally, the phenomenon of fatigue lacks clarity.[20] Considering the point that nurses, specially female nurses, are exposed to various psycho-somatic stressors interfering with their working ability and functioning as the cause of fatigue, some research aiming at analyzing the factors related to insufficient working ability and understanding their perceived fatigue is mandatory.[11] To develop a positive constructive work environment, it is further vital to obtain a better understanding of the degree to which nurses and other health-care providers are affected by conditions such as fatigue, burnout, and weariness.[13] Identification of nurses specific needs based on their demographic and occupational characteristics can be helpful in developing appropriate programs aimed at reducing fatigue. The findings of these programs may be applied in improving the nurses personal hygiene, stress management strategies, and development of fatigue management.[9]

The present survey focused on determining the perceived fatigue in female nurses and identifying the individual and occupational factors affecting this fatigue so that some appropriate measures could be taken to reduce fatigue in nurses through the exact identification of those factors. In this way, the quality of nursing care could be promoted and the nursing errors may be decreased.

METHODS

The present survey was a cross-sectional study conducted on the female nurses employed in the clinical wards of the teaching hospitals of Yazd, Central Iran, 2014. Sampling was done using the stratified multistage sampling method. To do so, first the hospitals were considered as strata. Then, a specific share (ratio) proportional to the sample volume was given to each hospital with regard to the percentage of the female employed nurses at that hospital compared to the total number of nurses in all hospitals. It should be mentioned that all the wards in each hospital were taken into account and the nurses in each ward were selected randomly based on the list of personnel and proportional to the number of the female nurses employed in that ward. Sample volume was estimated to be 270 nurses regarding the previous studies,[22] the sample's attrition rate of 15% and considering the prevalence rate of 18%, accuracy of 5%, and confidence level of 95%.

$$n = \frac{z^2.p(1-p)}{d^2} = \frac{(1/96)^2 \times 0/18 \times 0/82}{(0/05)^2} = 226$$

The inclusion criteria were: being female, holding at least a Bachelor of Sciences (BS) in nursing, full-time employment in a hospital, and at least one-year work experience. In the case that the nurses were not inclined to participate in the study, they were excluded from the survey. A two-part questionnaire

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was used to cull the data. The first part included demographic information such as age, marital status, having a suckling, and husband's support. The second part contained occupational parameters including work experience, work hours per month, post of duty, type of work shift (round), employment status, and having a second job. To investigate the rate of fatigue, the Iowa Fatigue Scale (IFS) was used which studied the degree of fatigue over the past month. This scale included 11 items each with a score ranging from 1 to 5 (never, a little, moderate, much, very much). This scale has been derived from integration and condensation of many of the available scales on fatigue. It has been proved to be a useful valid clinical instrument for screening and monitoring chronic fatigue.[23]

Generally speaking, a score between the ranges of 30-39 indicates the presence of considerable fatigue and a score of 40+ reveals severe fatigue. Hence, the cut-off point for a fatigued nurse was the one who scored 30+ on this scale. To establish the validity and reliability of this instrument, the recommended Forward-Backward method was used and the translated version was approved through consultation with three English language PhD's and psychologists.

Then, it was tested in a pilot study. The reliability of the questionnaire was r=0.82 using test-retest reliability coefficient on 20 nurses within 2 weeks. Also, Cronbach α was used to estimate the internal consistency coefficient of the items in the instrument which was 0.70. To carry out the survey, the researchers presented to the nurses in person in their working shift and the research procedures and objectives were explained to them. Having obtained their informed written consent, they were given the questionnaire and they completed it using self-report technique and handed it to the researcher during their next work round. The data were collected and analyzed using SPSS16 *via* descriptive and inferential statistics of independent T-test and one-way analysis of variance (ANOVA) and, Pearson correlation coefficient.

RESULTS

All the nurses participating in the survey completed the questionnaire and handed it to the researchers, so, the return rate of the questionnaire was 100% indicating the high importance of the issue for the female nurses. In fact, they were highly anxious about their fatigue to be reflected to the related authorities. The statistical findings pertaining to individual and occupational characteristics revealed that the mean and standard deviation (SD) of nurses age was 32.63±6.301 years, working experience 9.15±6.262 years, and work hours 184.81±26.698 h/month. Furthermore, regarding marital status, most female nurses (218, 80.7%) were married, most (153, 56.7%) were formally or permanently employed, most (252, 93.3%) held the post of a nurse, most (231, 85.6%) had circulating shifts, 12 nurses (4.4%) had a second job, and 59 nurses (21.9%) had a baby. The overall mean of nurses fatigue was 30.78±7.90. Independent T-test showed that there was a statistically significant difference between mean and SD of fatigue in permanent and temporary employment (p=0.01). Also, ANOVA revealed that there was a significant difference between mean and SD of fatigue at various levels of husband's support (p=0.000). Furthermore, using least significant difference (LSD) test, it was demonstrated that there was a significant difference between no support and little support (0.013), no support and much support (0.026), little support and much support (0.000) and moderate support and much support (0.000). Nevertheless, independent T-test showed that there was no statistically significant difference between mean and SD of fatigue between the married and single nurses (p=0.23), special and non-special wards (p=0.59), head nurse and nurse (p=0.51), fixed morning shift and circulating shift (p=0.21), having or not having a baby (p=0.10), and having or not having a second job (p=25) (Table 1). Based on data analysis, Pearson correlation coefficient demonstrated that there was a significant difference between the mean and SD of "fatigue and age" (0.008), and "fatigue and work experience" (0.02); however, there was no significant difference between the mean and SD of fatigue and work hours per month (0.38) (Table 2).

DISCUSSION

Our findings indicated that fatigue was higher than the cut-off point in the "considerable fatigue interval" among the female nurses employed in the clinical wards of the teaching hospitals of Yazd, Central Iran. Similar, studies also report moderate to severe fatigue among nurses. According to other study, nurses experience high rates of fatigue.[24] Besides, researchers reported that nurses in special wards experienced high levels of compassion fatigue.[25] In the study by Amaducci and colleagues,[26] 83.5% of the nursing students had moderate to severe fatigue with varying range of effects on the activities of daily living (ADL), the main cause being academic activities. Since individual's life style, culture, and organizational policies affect the prevalence and severity of work fatigue, and the prevention of work fatigue demands multi-dimensional approaches including involvement of the organization, clinical unit, and the individual,[24] developing support systems for nurses with fatigue and burnout is rendered as mandatory.[27]

Consequently, the managers of the health system of the country should take some appropriate measures to remove the material and spiritual shortcomings and deficiencies present in the system that induces fatigue in the employees. Indeed, in a study, sleep and recreation are the most important strategies for reducing fatigue.[26] Researchers offer aerobic exercises and sports to manage physical fatigue and mental burnout.[28] Strategies such as risk management education in continuous medical education programs have been recommended for reducing fatigue.[17] Hence, regarding the prevalence of fatigue among nurses, the predisposing factors should be considered meticulously. Also, both work environment variables and organizational factors (work conditions, interpersonal interactions in the work milieu, satisfaction, and occupational safety) and external variables out of the work environment must be taken into account with

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Demographic and Occupational Variables		No.	Percentage	Mean	SD	T-test
Marital Status	Single	52	19.3	29.60	8.612	T=1.23 P=0.23
	Married	218	80.7	31.06	7.721	
Employment Status	Permanent	153	56.7	31.81	7.471	T=2.47 P=0.01
	Temporary	117	43.3	29.43	8.278	
Type of Ward	General	181	67.0	30.60	8.243	T=0.53 P=0.59
	Special	89	33.0	31.15	7.199	
Post of Duty	Head nurse	18	6.7	29.61	6.482	T=0.64 P=0.51
	Nurse	252	93.3	30.86	8.001	
Work Shift	Fixed Morning	39	14.4	30.57	8.019	T=1.04 P=0.29
	Circulating	231	85.6	32.00	7.164	
Having a Suckling	Yes	59	21.9	32.27	8.310	T=1.64 P=0. 1
	No	211	78.1	30.36	7.757	
Second Job	Yes	12	4.4	30.90	7.891	T=1.13 P=0.25
	No	258	95.6	28.25	8.114	
Husband's Support	Never	66	24.4	35.41	7.176	F=7.238 P=0. 000
	Little	22	8.1	31.93	7.065	
	Moderate	107	39.6	30.71	8.693	
	Much	75	27.8	27.83	7.584	

Table 1: Comparison of mean and SD of fatigue in terms of demographic and occupational variables.

Demographic and Occupational Variables	Mean	SD	Correlation coefficient	*p*-value
Age	32.63	6.301	0.162	0.008
Work hour/month	184.64	26.595	0.054	0.38
Work experience	9.15	6.262	0.135	0.02

Table 2: Correlation coefficient between nurses fatigue score and demographic and occupational variables.

sufficient scrutiny.[27] In addition, other researcher recommends the analysis of effective variables and organizational factors related to fatigue.[17]

Moreover, the findings of our study regarding the correlation between fatigue and individual's traits demonstrated that fatigue was more prevalent in the married female nurses compared to the singles which was an expected result as married women have the occupational responsibility added to the familial duties. However, the difference was not significant. According to Sahebi and Ayatollahi,[29] marital status, i.e., married, single, divorced, or dead, had no correlation with mental health. Yet, being single was correlated with nurses vulnerability to occupational burnout in Spain.[25] It should be mentioned that most marriages in Iran occur below the age of 25 years increasing the vulnerability of married women. Based on our findings, there was a significant positive correlation between age and fatigue. In other words, younger individuals suffered less from fatigue and the perceived fatigue increased with age. This is because with increasing age, the expectations of satisfaction with work increases while the physical and psychological ability decreases. So, if the satisfaction is not achieved, more fatigue will be perceived.

Tanaka and colleagues[30] cite that age is directly correlated with fatigue. Furthermore, the age of 30+ was associated with vulnerability to occupational burnout in Spanish nurses.[25] Nonetheless, Amaducci and colleagues[26] assert that there is a negative correlation between age and fatigue, as older individuals are more compatible with facing new situations and suffer from fatigue to a lesser degree. Also, nurses with a suckling perceived fatigue more compared to those without a suckling indicating that caring for a suckling leads to increased perceived fatigue due to the demand for the responsibility of the suckling care, though of course the correlation was not significant. As Sahebi and Ayatollahi[29] declare, there was no association between number of children and mental health. The findings of this study showed that nurses who enjoyed their husband's support, perceived less fatigue. Nurses without any husband support perceived the most fatigue, those with little husband support per-

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ceived moderate fatigue, and those with much husband support perceived the least fatigue. There was a significant correlation between fatigue and husband's support. Peters and colleagues[31] recommend the study of home and familial characteristics as an effective predictor of health consequences in nurses. Social support exerts a positive effect on fatigue and burnout.[32] However, the findings of the study by other researcher are inconsistent with these results as unexpectedly they found no correlation between fatigue and individual's life partner.[26] Of course, they studied fatigue in nursing students which are different from our participants who were female nurses mostly married. In this case, the nurses life partner, specially their espouses, play a significant role in feeling less fatigue through spiritual support and even providing occupational facilities and essentials for their wives occupation.

Our findings regarding the association between fatigue and work traits revealed that fatigue was more prevalent in women whose employment status was guaranteed compared to those with temporary employment without any warranty and the difference between the 2 was significant. This may be due to the fact that the employed nurses knew that they should work for long years and tolerate hard work for that time to achieve a stable guaranteed occupational status, i.e., they needed a longer work experience. These factors caused the older nurses to perceive more fatigue compared to the younger ones with temporary employment. There was a significant positive correlation between fatigue and work experience so that nurses with longer work experience perceived more fatigue. There was a correlation between a work experiences longer than 10 years and nurses vulnerability to occupational burnout.[25] Hence, researchers introduce work experience as an important criterion in selecting the target group for implementing the required interventions to increase work stress coping skills.[13]

Regarding type of ward/unit, nurses were employed in special wards percieved fatigue more than those in general wards as they dealt with very ill in-patients who needed more intensive care. This caused them more fatigue, yet, the difference was not significant. Therefore, it is inferred that the severity of fatigue is also considerable in general wards and, on the whole, the clinical setting brings about fatigue in nurses due to type of activities and nursing care. Regarding post of duty, staff nurses felt more fatigue than head nurses. This may be due to the point that the head nurses have a fixed morning shift with a more regular work program. Besides, they are more involved in managerial than clinical affairs, so, they perceive less fatigue. Yet, the correlation was not significant. As for work shift, the women employed in fixed morning shift perceived less fatigue than those with circulating shift. As a rule of thumb, nurses with a circulating shift report more fatigue due to reasons such as irregular circadian rhythm, insomnia and insufficnet sleep, etc., yet, the association between the two was not significant. Sahebi and Ayatollahi[29] report no correlation between work shift and mental health. However, Palhars and coworkers[33] reports no association between work shift type and experience of disease and sleep quality among the participants, also Punja and colleagues[10] cite that individuals with circulating shifts experience fatigue by 19-29% while fatigue may be aggravated by increased sequential shifts and working for more than four 12-hour shifts.[34] Additionally, work shifts longer than 12 h are linked to increased fatigue and error.[24] Nurses working in 12-hour shifts get more drowsy and fatigue.[35] Female nurses with a second job other than nursing or those who worked as a nurse in several places perceived more fatigue compared to those with only one work shift, yet, the correlation was not significant. According to Zamanian and coworker[36] increased work load from the previous years has led to extensive fatigue among nurses. With regard to the relationship between work hours and fatigue, nurses with less work hours felt less fatigue while those with longer work hours or overwork reported more fatigue. Of course, it should be mentioned that work hours in Iran is 44 h/week. This was the mean work hour of the nurses under study indicating the obligation for working extra hours, yet, the correlation was not significant. In this respect, Sahebi and Ayatollahi[29] assert that long work hours are not correlated with mental and psychological health. In any case, the researchers recommend reducing work hours among the hospital personnel as a useful strategy for protecting nurses health.[37]

CONCLUSION

Based on the findings of the present study, female nurses employed in the clinical wards of teaching hospitals perceive considerable fatigue. Factors that show a significant correlation with fatigue include older age, being married, formal or permanent employment, and husband's little support. These demands more prompt interventions to improve the status of the female nurses with the above-mentioned condition. Overall, it is recommended that special attention be given to nurses general health and to the prevention of fatigue in female nurses by providing free leisure time activities and recreation, increased occupational support, and provision of consultation services. The 100% return of the questionnaires was one of the strong points of this survey. One of the limitations of this survey was that the participants education level was not studied as a variable since most of the nurses under study held a BS in nursing; so, a comparison of different educational levels was not possible. Moreover, as the concept of fatigue is multi-factorial, it was not plausible to investigate all the factors affecting it in one single questionnaire. This requires further research. It is also advisable to focus future research on elucidating the effects of strategies used to remove nurses fatigue.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Research

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Efficacy of a Multiple Health Behavior Change Intervention on Women's Health Outcomes

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ABSTRACT

Objective: Examine the efficacy of a 60 day autophagy-activating multiple health behavior change (MHBC) intervention that targets exercise, diet, sleep, and skincare on women's health outcomes.
Design: Using a single-arm intervention, 34 women (age range=30-55 years) completed both subjective self-report assessments (i.e., health-related quality of life, sleep quality, body satisfaction, and skin satisfaction) and objective assessments of body composition (i.e., BOD POD), blood pressure, heart rate, and skin health (i.e., dermatologist skin ratings) at day 0, day 30, and day 60.
Results: We found significant improvements from day 0 to day 30 to day 60 for the objective assessments of body composition (F=23.48, p<.001) and wrinkles (F=57.72, p<.001); and the subjective assessments of body satisfaction (F=23.03, p<.001), skin satisfaction (F=20.29, p<.001), and overall health-related quality of life (HRQOL) (F=5.27, p<.01). We found significant improvements from day 0 to day 60 for the subjective assessment of sleep quality (F=5.90, p<.007) and the objective assessments of heart rate (F=3.70, p=0.04) and systolic blood pressure (F=2.41, p<0.01).
Conclusion: A sixty day MHBC intervention improved women's targeted health outcomes of body satisfaction, skin satisfaction, sleep quality, aspects of health-related quality of life, heart rate, systolic blood pressure, and body composition. A randomized controlled trial with long-term follow-up in a variety of populations is needed to further determine the efficacy of this MHBC intervention.

KEY WORDS: Physical activity; intermittent fasting; skin.

ABBREVIATIONS: MHBC: Multiple Health Behavior Change; BMI: Body Mass Index; SPF: Sun Protection Factor; IRB: Institutional Review Board; PAR-Q: Physical Activity Readiness-Questionnaire; BASS: Body Area Satisfaction Scale; PSQI: Pittsburgh Sleep Quality Index; HRQOL: Health-Related Quality of Life.

INTRODUCTION

The highest morbidity and mortality due to chronic diseases (e.g., diabetes, cancer, heart disease, and obesity) are strongly associated with a number of health behaviors.[1] Modifiable lifestyle behaviors (e.g., diet, exercise, tobacco use) explain the majority of chronic diseases and account for 60% of all deaths across all demographics and geographic regions.[2] Health-promoting behaviors that characterize a healthy lifestyle can reduce both the emotional and the economic burden of chronic diseases.[3] If successful, the widespread adoption of a multiple behavior healthy lifestyle is estimated to save over $16 billion in annual medical costs.[4]

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Prospective studies reveal that healthy lifestyle behaviors such as regular physical activity, cancer screening, non-smoking/cessation, low alcohol intake, a healthy diet, and normal body mass index (BMI) increase longevity.[5-7] Moreover, adopting 3 health promoting behaviors is estimated to reduce chronic disease by over 70%.[6] Higher quality of life is also positively impacted by lifestyle, with those adopting four healthy behaviors being 7 times more likely to rate their health as excellent than people reporting no healthy behaviors.[8]

Health behaviors are inter-related in terms of the psychological, social, and environmental factors that reinforce them, and multiple unhealthy behaviors often coexist. Indeed, statistics reveal that American adults do not meet the minimum guidelines for many health behaviors. For example, more than 33% of American adults do not meet the recommendations for physical activity,[9] only 24% of adults consume the recommended servings of fruits and vegetables, over 66% of adults are either overweight or obese, about 35% of adults get insufficient amounts of sleep, and only 31% of adults use lotion that has an SPF of 15 or higher.[10] Interventions targeting multiple behaviors simultaneously offer the most promise for sustained behavior change.[11]

Multiple health behavior change (MHBC) interventions are a relatively new method of initiating lifestyle change that can advance health promotion, increase health benefits and quality of life, and reduce healthcare costs.[12,13] The results and conclusions that are drawn from this research are more applicable to everyday life because most people demonstrate multiple health behaviors, or multiple health-risk behaviors. Thus, it is reasonable to create an intervention that targets multiple aspects. Indeed, a person cannot alter one behavior without affecting another one, whether it is intentional or not, thus it is logical to focus on intentionally changing multiple factors at once.

MHBC, which typically focus on special populations, reveals that targeting multiple behaviors may result in more effective health behavior change.[14,15] Typically, MHBC interventions target changing two health behaviors, with a focus on diet and exercise, despite the fact that the presence of multiple risk behaviors has an additive or synergistic negative influence on health. For example, having both a poor diet and being physically inactive greatly increases the likelihood of obesity, diabetes, cancer, and cardiovascular disease.[16]

Thus, the purpose of our study was to conduct a MHBC intervention focusing on improving the following four health behaviors in adult women: Exercise, diet, skincare, and sleep. The goal of this MHBC intervention is to optimize autophagy. The term autophagy means self-eating, and refers to the processes by which your body cleans out various debris, including toxins, and recycles damaged cell components. We hypothesized that changing these four health behaviors would have significant improvements on women's body composition, body satisfaction, skin satisfaction, sleep quality, health-related quality of life, and skin health (i.e., wrinkles).

METHODS

Procedures

Prior to study participation, the women completed the Institutional Review Board (IRB) approved informed consent and the physical activity readiness questionnaire (PAR-Q) which is a self-screening tool to determine readiness to start an exercise program.[17] Eligible women were then provided with a detailed description of the 60 day MHBC intervention. The following assessments were take on day 0, day 30 and day 60: Subjective self-report questionnaires (i.e., Body Area Satisfaction Scale (BASS), Skin Satisfaction Scale, Pittsburgh Sleep Quality Index (PSQI), and Health-Related Quality of Life (HRQOL)), and objective assessments of body composition (i.e., BOD POD), facial photos taken by a photographer, and vital signs (i.e., blood pressure and heart rate). Each assessment took about 30-45 min to complete. Thirty five women were enrolled in the intervention. One woman dropped out of the study after the 30 day assessments due to a health concern unrelated to study participation. This represented an adherence rate of 97%.

Measures

Subjective assessments

Body area satisfaction scale: This eight-item scale asks participants to indicate their degree of satisfaction and dissatisfaction with discrete body features such as the face, hair, mid torso, upper torso, muscle tone, height, and weight on a Likert scale anchored at the extremes with 1 (very dissatisfied) to 5 (very satisfied).[18] The Body Areas Satisfaction Scale has good psychometric properties and in this study the internal consistency was excellent across the 3 assessments (day 0 α=.92, day 30 α=.88, day 60 α=.93).

Skin satisfaction scale: This ten-item scale assesses satisfaction with the following 10 facial skin areas: Firmness, complexion, glow, pores, youthful appearance, fine lines, elasticity, wrinkles, smoothness, crow's feet, tone, and overall skin satisfaction on a Likert scale anchored at the extremes with 1 (very dissatisfied) to 5 (very satisfied).[19] This scale has good psychometric properties and the reliability in this study was good (day 0 α=.82, Day 30 α=.86, day 60 α=.85).

Health-related quality of life (HRQOL): HRQOL was assessed with the 4-item Centers for Disease Control (CDC) health days module. Participants rated their perceived overall general health by indicating if their general health was excellent, very good, good, fair, or poor. Other items on this questionnaire required the participants to indicate the number of days within a month that they felt a certain way. For example: "Now thinking about your PHYSICAL HEALTH, which includes physical illness and injury, how many days during the past 30 days was your physical

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health NOT good?". This scale has good psychometric properties.[20]

Sleep quality: Sleep quality was assessed with the following single item from the Pittsburgh Sleep Quality Index: How would you rate your sleep quality overall. Participants used the following Likert type scale to indicate their sleep quality: 1=very good, 2=fairly good, 3=fairly bad, 4=very bad.[21] This scale has good psychometric properties.[22]

Objective assessments

Body composition: Body composition was assessed using the BOD POD which uses air-displacement plethysmography to estimate participant's fat-free mass, fat-mass, percent body fat, and body mass. The BOD POD assesses weight or body mass by assessing both fat-free mass and fat mass. Fat-free mass includes internal organs, bone, muscle, water, and connective tissue. In comparison, fat mass is the portion of the body that is composed of fat. Participants were measured while wearing tight-fitting clothing (e.g., Lycra swimsuit or compression clothing) according to standardized procedures, and manufacturer's guidelines were followed for the BOD POD assessment.[23]

Vital signs: Blood pressure and heart rate were electronically assessed.

Wrinkle severity: Wrinkle severity was assessed by a board certified dermatologist using a 6-point ordinal photonumeric scale on the facial photos that were taken by a professional photographer at day 0, day 30, and day 60. Severity was graded on a 0 (low wrinkles) to 5 (high wrinkles) scale.[24]

Intervention

Typically, MHBC interventions focus on changing diet and exercise, despite the fact that the presence of multiple risk behaviors has a negative influence on people's health.[25] Thus, the purpose of this intervention was to conduct a MHBC intervention focusing on synergistically improving the following four health behaviors in women: exercise, diet, skincare, and sleep.

The intervention for each health behavior was developed with a goal of activating autophagy.[25,26] The exercise consisted of four 30 minute sessions per week with a personal trainer. These sessions included high intensity interval and resistance training. The diet consisted of intermittent fasting in which the participants fasted for 16 hours and then return to their regular diet for 8 hours, all the while focusing on protein cycling. This pattern was followed for 3 days out of the week. For sleep behavior the participants were provided with healthy sleep hygiene education. Finally, for skincare the women followed an autophagy activating skincare regimen twice a day (morning and night) that consisted of a cleanser, brightening serum, an essence spray, a booster, a day cream, and a night cream.

RESULTS

Participants

Participants were a convenient sample of 34 women (*M* age=44.12, *SD*=5.93). Most of the participants were Caucasian (*n*=25), followed by African American (*n*=5), Hispanic (*n*=2), Asian (*n*=1), and other (*n*=1). The majority of participants had a household income of $120,000 and over (*n*=18), followed by $80,000-$120,000 (*n*=7), $50,000-$80,000 (*n*=7), and less than $50,000 (*n*=2).The participant's average BMI was in the overweight range prior to starting the intervention (*M*=28.25, *SD*=7.08).

Subjective Assessments

We found a significant improvement in the participants, skin satisfaction scale scores from day 0 to day 30 to day 60 (F=20.29, p<.001; See Figure1). We also found a significant improvement in the women's body areas satisfaction scale scores from day 0 to day 30 to day 60 (F=23.03, p<.001; See Figure 2). As well, sleep quality had a significant improvement from day 0 to day 60

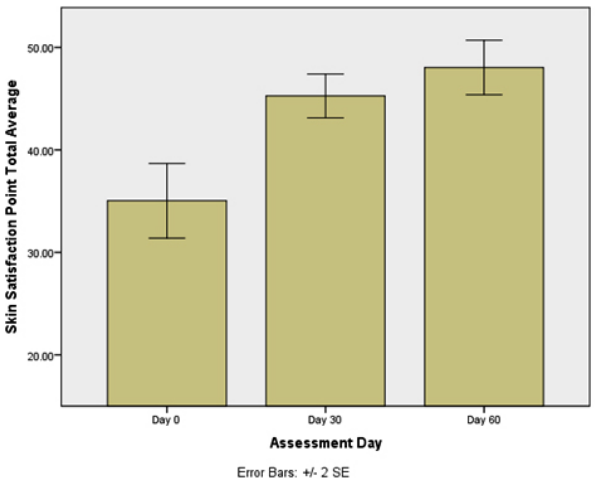

Figure 1: Significant improvement in skin satisfaction scale scores from day 0 to day 30 to day 60 (F=20.29, p<.001).

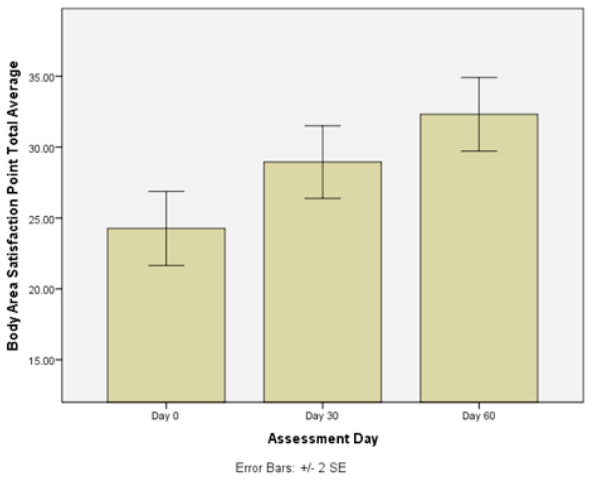

Figure 2: Significant improvement in body area satisfaction scale scores from day 0 to day 30 to day 60 (F=23.03, p<.001).

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Item	Day 0	Day 30	Day 60
	M (SD)	M (SD)	M (SD)
Sleep Quality**	2.11 (0.81)	2.13 (0.86)	1.88 (0.65)
Facial Wrinkles*	4.05 (0.54)	3.60 (0.59)	3.17 (0.57)
Skin Satisfaction Scale*	35.32 (8.93)	45.27 (5.46)	47.31 (6.92)
Body Area Satisfaction Scale*	24.47 (5.62)	28.56 (5.86)	31.43 (5.68)
Body Fat %*	36.85 (8.80)	35.81 (8.60)	33.20 (8.98)
Fat Free Mass (lbs) **	104.30 (16.45)	104.98 (16.44)	106.00 (16.33)
Fat Mass (lbs)*	66.74 (32.84)	61.50 (31.44)	57.63 (31.08)
Mass (lbs)*	171.04 (44.28)	166.48 (42.51)	163.63 (43.02)
BMI*	28.25 (7.08)	27.91 (6.91)	27.65 (6.81)
Systolic BP**	127.31 (20.71)	123.19 (18.73)	122.00 (19.01)
Diastolic BP	83.81 (12.68)	83.00 (13.06)	83.42 (14.61)
Heart rate**	74.27 (16.89)	73.62 (12.56)	70.23 (12.40)

Notes: BP=Blood pressure; BMI=Body mass index; lbs=Pounds
*Significant differences between day 0, day 30, and day 60
**Significant differences between day 0 and day 60

Table 1: Descriptive statistics for the study outcomes.

(F=5.90, p<.007; See Table 1).

We found a significant improvement in the women's overall HRQOL from day 0 to day 30 to day 60 (F=5.27, p<.012), with the average rating of HRQOL being "good" for the day 0 assessment and improving to "very good" by the day 60 assessment. A significant improvement was also evidenced in the women's mental health over the course of the intervention (F=3.63, p>.04). We also found a non-significant improvement in the women's physical health (F=0.35, p=.71) and the number of days that poor physical or mental health interfered with usual activities (e.g., self-care, work, or recreation (F=2.79, p=.07; see Table 2).

Objective Assessments

With regard to skin health, the women had a significant reduction in facial wrinkles from day 0, to day 30, to day 60 (F=57.72, p<.001).

Regarding body composition, we found a significant decrease in body mass (total lbs) of 7.41 lbs from day 0 to day 30 to day 60 (F=4.97, p=.01, see Table 1). We found a significant decrease in fat mass of 9.11 lbs from day 0 to day 30 to day 60 (F=16.69, p<.001). Regarding fat-free mass, the women had a significant increase of 1.70 lbs from day 0 to day 60 (F=8.91, p<.001). Finally, a significant decrease of 3.65% was evidenced in the women's % body fat from day 0 to day 30 to day 60 (See Figure 3; F=23.48, p<.001).

The women's resting heart rate improved significantly from day 0 to day 60 (F=3.70, p=0.04). We found a significant improvement in systolic blood pressure from day 0 to day 60 (F=2.41, p<0.01. There was no significant time change for diastolic blood pressure over the duration of the intervention (F=0.19, p=0.82).

DISCUSSION

We found that this MHBC intervention, whose underlying development focuses on activating the processes of autophagy at a cellular level, significantly improved women's body composition and health outcomes. Study findings, study limitations, and future research directions are discussed below. First, we found

Item	Day 0 M (SD)	Day 30 M (SD)	Day 60 M (SD)
Now thinking about your PHYSICAL HEALTH, which includes physical illness and injury, how many days during the past 30 days was your physical health NOT good?	4.94 (8.05)	4.83 (6.57)	4.06 (6.30)
*Now thinking about your MENTAL HEALTH, which includes stress, depression, and problems with emotions, how many days during the past 30 days was your mental health NOT good?	7.6 (7.89)	5.96 (8.72)	4.78 (6.42)
During the past 30 days, how many days did POOR PHYSICAL OR MENTAL HEALTH keep you from doing your usual activities, such as self-care, work, or recreation?	2.60 (4.31)	3.33 (6.16)	1.91 (4.11)

*Significant differences between day 0, day 30, and day 60

Table 2: Health-related quality of life scores from day 0 to day 30 to day 60.

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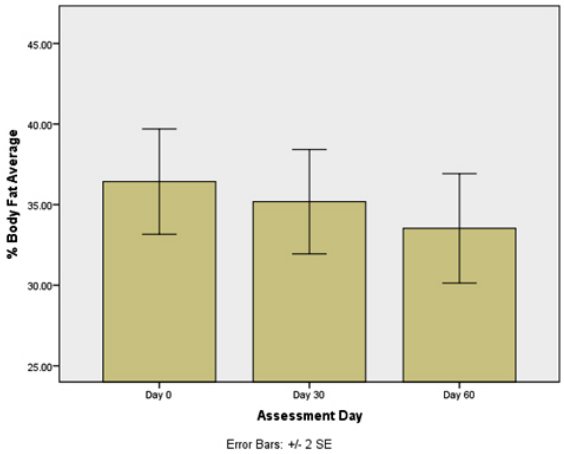

Figure 3: Significant improvement in % body fat % on from day 0, to day 30, and to day 60 (F=23.48, p<.001).

that the women had significant improvements in their wrinkles as assessed by a board certified dermatologist. In other words, the depth and length of the women's fine lines and wrinkles decreased over the course of this intervention. Not surprisingly, the women also self-reported an improvement in their skin satisfaction. In short, daily use of the autophagy activating topical skincare products resulted in continual improvements in the women's skin health (i.e., fine lines and wrinkles) after 30 and 60 days of use.

Second, using the BOD POD as an objective assessment, we found that the women's body composition improved significantly over the duration of the intervention. Over the course of the intervention, the participants lost an average of almost 7½ lbs of weight. More specifically, however, the women gained over 1½ lbs of fat-free mass(portion of the body that consists of internal organs, bone, muscle, water, and connective tissue) and lost an average of over 9 lbs of fat mass (portion of the body that is composed of fat) over the course of the intervention. The increase in fat-free mass is most likely attributed to the HIIT and resistance training that the women engaged in over the course of the intervention.

With regard to % body fat, the women's average % body fat was in an excess fat range at the beginning of the study (excess fat range=30.1% to 40%). By day 60 of the intervention the women had lost an average of 3.65% body fat and their body fat rating was approaching a healthier range. Not surprisingly, the women also had a significant improvement in their body satisfaction over the course of the intervention.

Third, the women's resting heart rate decreased significantly by an average of 4.01 beats a minute by the end of the intervention. A normal resting heart rate for adults' ranges from 60 to 100 beats a minute. Generally, a lower heart rate at rest implies more efficient heart function and better cardiovascular fitness. Our participants at day 0 had slightly high blood pressure. By day 60 they had an improvement in their systolic, but not diastolic, blood pressure. Of practical importance, at the end of the intervention their blood pressure was approaching the "ideal and healthy blood pressure" range.

In general, our study findings further illustrate that health behaviors are not independent but rather interrelated. Thus, targeting multiple modifiable health behaviors may be most effective for behavior change. In fact, targeting two health behaviors in an individual reduces medical costs by about $2,000 per year.[25] Consequently, targeting change in multiple health behaviors has the potential for greater health benefits, enhanced disease prevention, and reduced healthcare costs.

Strengths of our study include examining 4 health behaviors simultaneously. Typically, MHBC interventions focus on only 2 behaviors, usually diet and exercise. To our knowledge, this is the first MHBC intervention to focus on 4 health behaviors. Another strength is that the intervention for each health behavior was implemented with a goal of activating autophagy.[26,27] Likely due to their interdisciplinary nature, behavioral health scientists and practitioners are motivated to incorporate MHBC research concepts into their programs.[12] Among the MHBC interventions that have been conducted, this is the first lifestyle intervention that focused on altering four different health behaviors (i.e., exercise, diet, sleep, and skincare). Most other MHBC interventions only focus on two health behaviors, usually being physical activity and diet.[13]

Study limitations of our pilot research include a convenient nonrandomized small sample of motivated overweight women which reduces the generalizability of our findings. Randomized controlled trials, in a variety of populations (e.g., men, obese, older adults), with long-term follow-up are needed to further examine the efficacy of our study findings.

CONCLUSION

In conclusion, this MHBC intervention was efficacious for im-

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proving both objective and subjective health outcomes in the women. It had significant improvements on the women's overall body composition, body mass, % body fat, skin health, sleep quality, body satisfaction, and skin satisfaction. And although when compared to a single health behavior change intervention it requires more participant adherence and outcome measures 96% of health behavior experts indicate that MHBC interventions are "very-to-extremely important,".[13] Randomized controlled trials, in a variety of populations, with long-term follow-up are needed to further examine the efficacy of our study findings.

CONFLICTS OF INTEREST

Hausenblas H serves as a consultant for W products, who in part funded the study, but she does not receive royalties.

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Brief Research

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Cesarean Hysterectomy for Abnormal Placentation Using Balloon Occlusion of the Common Iliac Artery: Case Series

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ABSTRACT

Objective: To investigate the management and safety of cesarean hysterectomy using common iliac artery balloon occlusion (CIABO) for placenta percreta/increta/accreta.
Patients and Methods: We performed 4 cesarean hysterectomies at 33-36 weeks of gestation. All 4 patients had undergone cesarean section previously and had placenta previa. The patients then underwent cesarean hysterectomy using CIABO.
Results: Two patients were ultimately diagnosed with placenta percreta, one with placenta increta and 1 with placenta accreta. The actual invasive depth of the placenta tended to be deeper than had been diagnosed before surgery. The volume of blood loss in the 3 patients whose balloons were placed in the common iliac artery from the start ranged from 1361-3851 ml (including amniotic fluid and fewer amounts of bleeding than these), and these patients received only autologous blood transfusion. All 4 patients were ultimately discharged from the hospital without any complications.
Conclusion: We were able to control the blood loss well using CIABO during cesarean hysterectomy. We confirm that our method of managing cesarean hysterectomy for abnormal placentation can be conducted safely.

KEY WORDS: Cesarean hysterectomies; Common iliac artery balloon occlusion; Placenta percreta; Placenta accrete; Placenta accreta.

ABBREVIATIONS: CIABO: Common Iliac Artery Balloon Occlusion; IIABO: Internal Iliac Artery Balloon Occlusion.

INTRODUCTION

The rates of abnormal placentation, such as placenta accreta, increta, and percreta, have increased.[1,2] The condition in which the placenta invades the entire depth of the uterine wall is called "placenta percreta". Placenta accreta and increta are less severe variants of the same condition.[3,4] The major risk factors of abnormal placentation are a placenta previa and previous cesarean section.[5,6] The recent increased frequency of cesarean section has resulted in a high incidence of abnormal placentation.

Placenta accreta, increta, and percreta often result in massive peripartum hemorrhaging and are sources of maternal morbidity and mortality in modern obstetrics.[7-10] In particular,

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uterine rupture and profuse hemorrhaging have been associated with placenta percreta.[11] Placenta percreta represents the most difficult management situation of these disorders.

The options for treating abnormal placentation include both conservative and extirpative approaches.[12] The generally accepted treatment for the most severe form of abnormal attachment of the placenta is cesarean hysterectomy without attempts to detach the placenta. Recently, the role of interventional radiology in the field of obstetrical hemorrhaging has been widely investigated. Preoperative internal iliac artery balloon occlusion (IIABO) has been widely performed to reduce the blood loss during cesarean hysterectomy.[13-16]

We herein report the safe performance and management of cesarean hysterectomy using common iliac artery balloon occlusion (CIABO).

PATIENTS AND METHODS

Four patients who underwent cesarean hysterectomy at 33-36 weeks of gestation using balloon occlusion at Otsu Red Cross Hospital, (Shiga, Japan) from 2009-2013 were recruited for the study. We informed the patients and their families of all of the risks involved in the surgery. All the 4 patients had previously undergone cesarean section. They had placenta previa and myometrial involvement on old operation scars. The myometrial invasion depths of the placenta were determined on ultrasonography (US) and magnetic resonance imaging (MRI). All the 4 patients then underwent cesarean hysterectomy using CIABO (In one case, the balloon was moved from the internal iliac artery to the common iliac artery in order to reduce blood loss). The study protocol was approved by the ethics committee of Otsu Red Cross Hospital, Otsu, Shiga Prefecture, Japan.

Procedure of Cesarean Hysterectomy

Prior to the surgery, no infiltrations of the placenta into the mucosa of the urinary bladder were shown by cystoscopy, and bilateral ureteral stent-catheters were inserted by urologists. Under general anesthesia, the balloon catheters were inserted *via* the bilateral femoral arteries and fixed in the common iliac arteries in the operation room by radiologists (Figure 1). During cesarean hysterectomy, these balloons were not inflated. The surgeons started the cesarean section, followed by a vertical incision of the abdominal skin and transverse uterine fundal incision. In case 1 alone, the balloons were first fixed in the internal iliac arteries, but were subsequently moved to the common iliac arteries due to a large amount of blood loss.[17]

As soon as the child was born, the balloons in the bilateral common iliac arteries were inflated. The uterine incision was sutured without detaching the placenta. This was followed by performing a total abdominal hysterectomy as shown in Figure 1. The procedure entailed; ligating and cutting of the uterine arteries at the point of intersection with the ureter. Incision of recto-cervical fold of peritoneum was made to have access to the posterior vaginal fornix followed by a circumferential incision of the vagina at the level of the vaginal fornices. Ligating and cutting the bilateral round ligaments and ligament ovaries were performed. We then incised the left and right connective tissues of the uterus (the sites of ascending and descending branches of uterine arteries) in the upper direction. We were then able to remove the uterus completely. While repairing the incisions, the

Figure 1: Anatomy in the Pelvis and Cesarean Hysterectomy Procedure. For more Information, see the Text of this.

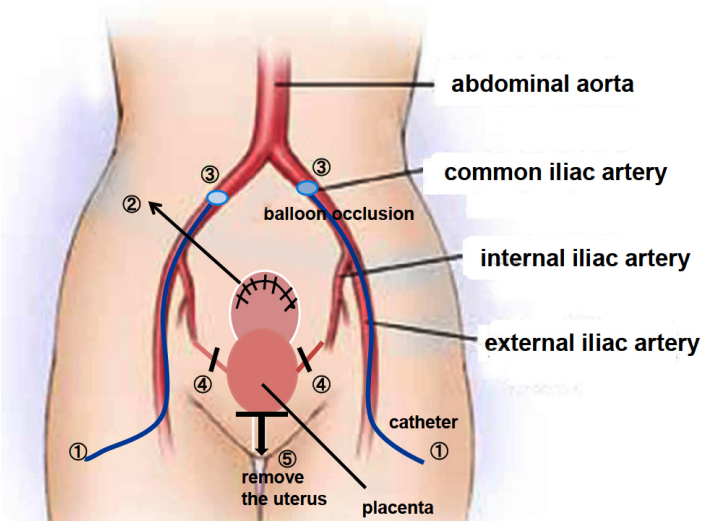

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Table 1: The Clinical Data of 4 Patients Treated with Cesarean Hysterectomy using Balloon Occlusion of the Common Iliac Artery.

Patient	Case 1[17]	Case 2	Case 3	Case 4
Age	36 yr	32 yr	35 yr	33 yr
Clinical diagnosis	Preg. 35 w 6 d previous 4 times c-sec total placenta previa s/o placenta increta	Preg. 35 w 5 d previous 1 time c-sec total placenta previa s/o placenta accreta	Preg. 36 w 0 d previous 1 time c-sec total placenta previa s/o placenta increta	Preg. 33 w 5 d previous 1 time c-sec total placenta previa s/o placenta accreta
Balloon position	internal iliac a. =>common iliac	common iliac a.	common iliac a.	common iliac a.
Occluded time	1 hr 15 min	56 min	50 min	55 min
Blood loss	7720 ml (including amniotic fluid)	3781 ml (including amniotic fluid)	3851 ml (including amniotic fluid)	1361 ml (including amniotic fluid)
Blood transfusion	Autologous blood 1200 ml MAP 10 iu, FFP 10 iu	Autologous blood 1050 ml	Autologous blood 1750 ml	Autologous blood 1200 ml
Complication	None	None	None	None
Surgical time	2 hr 49 min	3 hr 43 min	4 hr 25 min	2 hr 48 min
Pathologic diagnosis	Placenta percreta	Placenta increta	Placenta percreta	Placenta accreta

bilateral catheters were removed.

The success of these procedures was evaluated based on the amount of blood loss and presence of complications.

RESULTS

The clinical data of 4 patients treated with cesarean hysterectomy using balloon occlusion of the common iliac artery are shown in Table 1.

The patients' ages ranged from 32-36 years old (mean 34 years old). Two were ultimately diagnosed with placenta percreta, 1 with placenta increta and one with placenta accreta. There was only a case where the clinical diagnosis before surgery corresponded to the final diagnosis after surgery. The actual invasive depth of the placenta was deeper than that estimated before surgery in three cases. On comparing the diagnoses before and after surgery, the final diagnoses were worse after surgery in three cases. All of the placentas were attached to the old operation scars. However, the myometrial invasion depths of the placentas were found to have not been accurately determined on US and MRI.

As we previously reported, we were unable to control the massive bleeding with IIABO.[17] We therefore, immediately moved the balloon from the internal iliac artery to the common iliac artery. Because of our experience with case 1, we placed the balloon in the common iliac arteries from the start of the operation in cases 2-4.

Regarding the outcomes of cesarean hysterectomy, the total volume of blood lost was 7720 ml in case 1, 3781 ml in case 2, 3851 ml in case 3 and 1361 ml in case 4. The volume of blood lost in the 3 patients whose balloons were placed in the common iliac artery from the start of the surgery ranged from 1361-3851 ml (including amniotic fluid and fewer amounts of bleeding than these), and these patients received only autologous blood transfusion (1050 ml, 1200 ml and 1750 ml; mean 1333 ml). The time of occlusion of the common iliac arteries ranged from 50 min to 1h 15 min with intervals of 10 min for deflating the balloons.

Complications did not occur in any of the 4 patients treated with these methods and management strategies. Our staff (midwives and doctors) visited the patients many times and also supported their mental healing. The 4 patients were discharged from our hospital on the 7th or 8th post-operative day. Post-operative evaluation of the patients 30 days after the surgery did not reveal any complications with all mothers and children being in good health.

DISCUSSION

Although, the impact of morbidly abnormal placentation on pregnancy outcomes has been well-described, no randomized trials and few studies have examined the management of pregnancies complicated by this disorder. As a result, the recommendations for its management are based on case series and reports, personal experience and expert opinion.

The options for treating abnormal placentation include both conservative and extirpative approaches. O'Brien et al[12] reported that conservative treatment was preferred in hemodynamically stable patients. However, the patients treated with such conservative therapy are at continued risk of massive hemorrhaging and require prolonged intensive observation. Postpartum hemorrhage necessitating hysterectomy has been observed from 3 hours to 7 weeks after delivery in women who were initially managed conservatively.[18,19] In contrast, the extirpative approach is completed within a certain period and usually re-

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quires an adjuvant hemostatic technique, such as pre-operative placement of balloon occlusion.[13-16] In our hospital, we have safely performed cesarean hysterectomies using arterial balloon occlusion. The size of their balloons should be optimally tailored to the anatomically targeted vessels being occluded using pre-operative MRI, because a poorly occluded vessel will yield incomplete hemostasis and increased hemorrhage.[20]

As we previously reported in case 1,[17] we attempted to perform IIABO to treat patients with placenta percreta. However, massive vaginal bleeding suddenly occurred due to detachment of the placenta following uterine contraction during cesarean hysterectomy. A quick shift from IIABO to CIABO was very effective in reducing the volume of blood loss. The use of IIABO in patients has reported no improved surgical outcomes compared with patients without the treatment.[21,22] Failure of IIABO can be explained by the presence of extensive anastomosis bridging the internal and external iliac arteries.[23] We therefore, subsequently performed CIABO during cesarean hysterectomy (cases 2-4). Theoretically, proximal balloon occlusion of the large vessels such as the aorta and common iliac arteries is more effective for hemostasis. However, it is possible to cause the potential risk of ischemia to the extremities if prolonged occlusion is required in these cases.[20]

In cases 2-4, we were able to control the hemorrhage using CIABO during cesarean hysterectomy (range of blood loss: 1361-3851 ml including amniotic fluid). Regarding blood transfusion, we were able to use autologous blood alone in cases 2-4. In addition, all of the patients were discharged from our hospital without any complications, such as thrombus, embolism, coagulopathy, severe anemia, hematoma, infection or organ disorders. Balloon occlusion has been thought not to stop blood flow completely.[24]

While a few other reports have also described the superiority of CIABO to other methods,[23,25-28] rare cases complicated by thrombosis have been reported after CIABO, necessitating conservative managements with a heparin drip.[28-30] Therefore, the occlusion time should be as short as possible.

Following cesarean hysterectomy, the patients are at risk for complications, such as persistent coagulopathy, anemia, thromboembolism and other organ disorders, and death. As such, the patients may experience anxiety or even post-traumatic stress disorder. They may also experience pain, uterine loss, numbness, and issues in communicating or bonding with their baby. These patients therefore, require close monitoring, sometimes in an intensive-care setting.[31] Psychiatrists, special midwives and social workers should focus on the mental health care of these patients. We were unable to follow the patients for more than a month after surgery because we could not set up a system of the further examination. Understanding patients' experiences with emergency peripartum hysterectomy can help practitioners not only address patients' initial complications but also provide needed long-term support.[32]

CONCLUSIONS

CIABO during cesarean hysterectomy was effective in controlling blood loss in 4 cases and can be conducted safely. Given that only 4 cases were managed using this technique in this study, further evaluation of the efficacy and outcomes of CIABO is needed. Patients treated with cesarean hysterectomy should be managed by close monitoring in an intensive-care setting with ample support for their mental healthcare.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

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Cesarean Section and Associated Surgeries: Feasibility and Surgical Outcomes

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ABSTRACT

Cesarean section being the most commonly performed surgery in Egypt, the incidents of cesarean delivery in general hospitals were found to be nearly 50.6%, whereas, in private hospitals such cases were reported to be much higher. Many disorders, either gynecological or non-gynecological could coexist or precede a cesarean delivery. These disorders need to be managed surgically; invariably most patients will prefer to undergo a cesarean section with concomitant surgery for any associated pathology. The feasibility and complications of such dual surgeries have been addressed in this review article.

KEYWORDS: Cesarean section; Associated surgeries; Feasibility; Outcomes.

ABBREVIATIONS: WHO: World Health Organization; IUD: Intra-uterine devices; ACOG: American College of Obstetricians and Gynecologists; CIS: Carcinoma *In Situ*; AIS: Adenocarcinoma *In Situ*; CIN: Cervical Intraepithelial Neoplasia.

INTRODUCTION

The occurrence of cesarean deliveries in countries such as Egypt in the year 2014 (50.6%), was observed to have surpassed the World Health Organization (WHO) recommend.[1]

Many operations are now-a-days done simultaneously with cesarean sections, with different success rates and complications. These operations may be gynecological or non-gynecological as shown in Figure 1.

GYNECOLOGICAL SURGERIES

Uterine Surgeries with Cesarean Section

Myomectomy

Myomectomy during cesarean section is limited only to pedunculated myomas, because resection of myomas at the time of cesarean section usually stimulates profuse bleeding, requiring life-saving hysterectomy.[2-4]

Many researchers have studied the feasibility of myomectomy during cesarean section, either by developing new techniques for myomectomy or by devascularization techniques to reduce blood loss and to potentially eliminate multiple surgeries. However, many surgeons are still resisting this policy due to the lack conclusive evidence demonstrating its safety.[5]

Incebiyik et al[6] conducted a retrospective study including 16 patients who underwent myomectomy, concurrently with cesarean section, between January 2009 and September 2012. The pre- and post-operative hemoglobin values, number, size and total volume of excised fibroid

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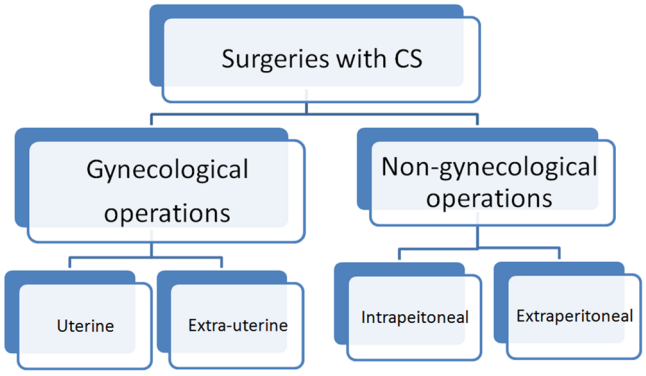
Figure 1: Types of Surgeries that could be done in Association with Cesarean Delivery.



nodules, location of fibroids, duration of operation, and duration of hospital stay of all patients were retrospectively investigated. They concluded that, myomectomy carried out during cesarean section is a safe surgical intervention regardless of the size of leiomyomata.

Awoleke et al[7] conducted a review study on myomectomy during cesarean section in Africa, with respect to the duration of surgery, blood loss, length of hospital stay, and blood transfusions. He found a limited number of studies in this issue owing to the fear of complications; however, the authors of the published studies concluded that the complications and morbidity following cesarean myomectomy do not significantly differ from those occurring during cesarean section alone, while fertility is apparently not compromised by this treatment. Success of procedure requires careful patient selection, adequate experience, and efficient haemostatic measures.

Simsek et al[8] conducted a retrospective study on 70 patients of cesarean myomectomy (Group 1) and compared the results with patients who underwent cesarean section alone (Group 2). The mean surgical time of the myomectomy Group was 58.1+/-23 minutes which was significantly increased (p<0.01). Mean post-operative hemoglobin value was 9.6+/-1.5 in the myomectomy Group and 10.8+/-1.01 in controls (p=0.01). Length of hospital stay was significantly longer in the myomectomy Group (p<0.05). Although, the procedure was related with increased blood loss, authors concluded that myomectomy during cesarean section is a feasible procedure without any serious complications or the need for blood transfusion.

Lee et al[9] conducted a study on 31 patients where myomectomy was performed during cesarean section. They developed a new purse-string suture allocated around myoma during cesarean section with the assistant maintaining strong tension on the purse-string suture around the myoma. They concluded that, purse-string suture method was effective and safe for more than 3 years and have not observed failures and serious complications, such as late hemorrhage and uterine rupture during a subsequent pregnancy.

Sapmaz et al[10] conducted a prospective study on 70 patients who underwent cesarean myomectomy, allocated in 2 Groups. The Group I included 52 patients who underwent cesarean myomectomy with systemic devascularization while Group II included 18 patients managed by tourniquet and served as a control. They stated that bilateral ascending uterine artery ligation and tourniquet use had similar outcomes with regard to intraoperative blood loss in cesarean myomectomy cases; however, the efficacy of ligation on blood loss in the post-operative period is superior to tourniquet method, since the tourniquet is removed at the end of the operation. Therefore, bilateral ascending uterine artery ligation may be preferable in cesarean myomectomy cases.

Desaiet al[11] used a novel technique of uterine devascularization in 17 patients before performing cesarean myomectomy, where the ascending and descending uterine arteries were ligated. Also, ligation of ovarian vessels, medial to the ovary was done. Not all patients required hysterectomy. No serious complications occurred and patients were discharged by the fifth day.

Holub et al[12] assessed pregnancy outcomes and deliveries after laparoscopic ligation of uterine artery during laparoscopic myomectomy. One hundred and fifty-three patients underwent ligation and transection of uterine arteries in that four-year study. The study concluded that laparoscopic transection of uterine vessels preserves the uterus, maintains ovarian blood supply and allows for the achievement of pregnancy in women with symptomatic fibroids. Fetal growth and umbilical Doppler findings remained normal in all cases.

The conclusion was that, with a good patient selection and expertise, cesarean myomectomy is safe and feasible.[13-22]

Intra-Uterine Devices (IUD) Insertion During Cesarean Section

Many researchers found that intra-cesarean section Intra-uterine devices (IUD) placement is better than interval insertion after 6 weeks, with comparable expulsion rates. Blumenthal and Gold-

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thwaite[23] highlighted the numerous benefits of intra-operative IUD placement, including proper access to the uterine and no additional cost or duration to the primary delivery procedure.[23]

Pelayo et al[24] conducted a prospective study which included 152 patients who underwent cesarean section. IUD were inserted in seventy-two patients during cesarean section, whereas the remaining 74 patients underwent cesarean section without IUD. Analysis of pain, bleeding and infection was done. Authors concluded that no difference in the results between both Groups was noticed and they recommended the insertion of the IUD during the cesarean section as a secure and helpful method for the fertility.

This was supported by the results of Halder et al[25] who evaluated and compared the safety and efficacy of vaginal and intra-cesarean insertion of post-partum intrauterine contraceptive device. They found that both modes of insertion were found to have very low rates of expulsion, vaginal bleeding, infection, missing strings, and also effective as contraceptive. Expulsion rate was 4% in the vaginal Group and 2 % in intra-cesarean Group. They concluded that, intra-cesarean IUD insertion is an appealing approach for post-partum contraception after cesarean delivery.

On the other hand, a study done by Sevki et al[26] concluded that insertion of IUD during cesarean section provides adequate protection against pregnancy. However, more than one fourth of the participants discontinued IUD use due to spontaneous expulsion or other medical reasons. Further studies concluded that, expulsion rate is higher with IUD insertion during cesarean section.[27] Other studies provided the solution of expulsion by either anchoring methods or by the use of frameless IUD.[28-30]

At the end of this section, it can be concluded that, the quality of evidence was moderate and trials of adequate power are needed to estimate expulsion rates and side effects. The benefit of effective contraception immediately after delivery may outweigh the disadvantage of increased risk for expulsion.[31]

Cesarean Hysterectomy

Cesarean hysterectomy is suggested mainly to prevent or treat postpartum hemorrhage due to uterine atony, placenta accreta, percreta invading bladder minimizing blood loss and saving the mother's life.[32] American College of Obstetricians and Gynecologists (ACOG) advised elective planned cesarean hysterectomy without any trial to remove the placenta, to minimize the risks associated with placenta accreta such as massive bleeding and associated risks of disseminated intravascular coagulation, infection, acute respiratory distress syndrome, renal failure, and death.[33]

Shellhaas et al[34] conducted a prospective, 2-year observational study at 13 academic medical centers between January 1, 1999, and December 31, 2000, on all women who underwent a cesarean hysterectomy. They found that 39,244 women underwent cesarean delivery with a total of 186 cesarean hysterectomies (0.5%). The causes for cesarean hysterectomy were: Placenta accreta (38%) and uterine atony (34%). The major complications associated with cesarean hysterectomy were: Blood transfusion (84%) and other blood products (34%), fever (11%), subsequent laparotomy (4%), ureteral injury (3%), and death (1.6%). Urinary complications were higher in cases of placenta accreta.

Another reason for peripartum hysterectomy was uterine rupture, either after vaginal delivery trial or due to previously scared uterus. Hysterectomy was indicated if hemorrhage persisted. Hysterectomy was either total or sub-total, depending on the site of rupture and the patient's condition.[35]

Cesarean Radical Hysterectomy

Another reason for cesarean hysterectomy is cancer during pregnancy which poses significant challenges to both the clinician and the mother. This is usually observed in pregnant women in forties, when the incidence of some of the common malignant neoplasm begins to arise. Although, pregnancy is characterized by extensive medical observation, a delay in diagnosis and lack of attention to the subtle presentation of malignancies, could lead to such cases.[36]

Some authors advocate intrapartum hysterectomy (following either vaginal or cesarean birth) to be performed for patients with carcinoma *in situ* (CIS) or adenocarcinoma *in situ* (AIS) who have completed their families and/or have proved to be noncompliant. Although, postpartum regression may occur with even CIS, some surgeons argue against the routine performance of an intrapartum hysterectomy for the management of cervical intraepithelial neoplasia (CIN) in pregnancy.[36]

Monk and Montz et al[37] studied the treatment of invasive cervical cancer, complicating intra-uterine pregnancy with radical hysterectomy. They identified 13 patients who underwent radical hysterectomy and bilateral pelvic lymphadenectomy with the fetus *in situ* and 8 others who underwent cesarean delivery followed by radical hysterectomy and bilateral pelvic lymph node dissection. The mean operative time was 281 minutes, and the mean blood loss was 777 mL for radical hysterectomy with the fetus *in situ* plus lymphadenectomy and 1750 mL when cesarean section preceded the cancer operation. The surgical morbidity was minimal for the whole Group, and after documentation of fetal maturation, seven healthy infants were delivered.[37]

Extra-Uterine Surgeries with Cesarean Section

Tubal sterilization

The most common operation done with cesarean section is tubal sterilization. Some patients, who have delivered vaginally before, prefer to undergo cesarean sterilization during the lastpregnancy.[38]

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Ozyer et al[39] conducted a study on 50 patients divided into 2 Groups, where Group I included 24 patients who had undergone tubal sterilization with cesarean delivery and Group II included 26 patients who had undergone tubal sterilization as a separate operation. They concluded that, tubal sterilization during cesarean section is more practical and safe than planned tubal sterilization alone.

Basava et al[40] conducted a study on five hundred multigravid women who underwent Cesarean section for various reasons and wanted concurrent tubal sterilization by either modified Pomeroy's technique or by Falope ring application. They reported one case of ectopic pregnancy with serious complications in a patient who underwent tubal sterilization by modified Pomeroy's technique.

Swendeet al[41] conducted a retrospective analysis of the clinical records of 78 patients who had undergone female sterilization in Makurdi. They concluded that a majority of female sterilization procedures were performed using cesarean section. The procedure was found to be safe and effective.

Salpingectomy

A retrospective analytical study was conducted at a tertiary care center from January 2010 to December 2014, in the Karnataka Institute of Medical Sciences, Hubli, Karnataka. The case files of all the patients who underwent the sterilization were taken from the medical records section and reviewed in detail. The cases were Grouped as cesarean tubectomy, minilaparotomy and laparoscopic sterilization, based on the technique used for abdominal entry. Out of 5442 cases of female sterilization, 2872 underwent cesarean tubectomy, while the remaining underwent minilaparotomy (1306) and laparoscopic sterilization (1264). They concluded that cesarean tubectomy is a safe and popular method, with more than half of the patients opting for it. Cesarean tubectomy can be offered to patients who undergo cesarean operation for obstetric indications and who desire a permanent method of sterilization.[42]

Another retrospective cohort study was conducted on women who underwent cesarean section performed in a single institution from December 2014 to January 2016. Operative reports were reviewed to confirm complete salpingectomy. A total of 171 patients were identified, who delivered *via* cesarean section with 50% of these patients proceeding with salpingectomy at the time of delivery. The salpingectomy completion rate was 96.4%. They concluded that salpingectomy at the time of cesarean delivery is feasible. Results from this study can be considered when managing a patient who desires sterilization and may also benefit from ovarian cancer risk reduction.[43] The same results were supported by Danis et al[44] who advised bilateral tubectomy at the time of cesarean section in the special population.

The shortcoming was that, with most cesarean deliveries, the removed segment of the fallopian tube is not examined for a histological diagnosis. Accordingly, it is important for the surgeon to verify the pathology report, which adds an additional component to the post-service work. The risks concerning the operative complications with this procedure are low, but real. The common risks are the failure to reach both tubes from extensive adhesions and broad ligament hematoma. Furthermore, sterilization failure occurs in about 1 in 100 cases even though the operation was performed properly. This failure also carries a liability risk. For the previously mentioned risks, FIGO does not approve of tubal sterilization during Cesarean section.[45,46]

Despite the ban of tubal sterilization by law in some countries, sterilizations continue to be performed during cesarean sections. The cause of the ban being that, cesarean sterilization contributes to the increase in cesarean sections.[47]

Ovarian Cystectomy

The reported incidents of adnexal masses during pregnancy vary from 1 in 81 pregnancies to 1 in 8000 pregnancies. There is still a debate regarding the management of incidental adnexal masses during the cesarean section considering the risk of this additional procedure on post-operative morbidity and mortality.[48]

Hobeika et al[48] reviewed the histopathology of 43 adnexal masses, incidentally diagnosed and excised during cesarean delivery. The histopathological diagnoses were: Mature cystic teratomas (34.9%), mucinous cystadenomas (16.3%) and serous cysts or cystadenomas (14.0%). Other histopathologies included: Endometriomas (11.6%), luteomas (7.0%), paraovarian cysts (4.7%), corpus luteum cyst (2.3%), fibroma (2.3%), inclusion cyst (2.3%), serous-mucinous cyst (2.3%) and borderline serous cystadenoma (2.3%). The authors concluded that ovarian tumors incidentally diagnosed and excised during cesarean delivery are rare and mostly benign. Also excision of such lesions should be considered.

Cengizet al[49] conducted a retrospective study by reviewing medical records of the patients who had incidental adnexal masses during cesarean section in Istanbul, Turkey. There were 38 cases of incidental adnexal masses which were discovered during the cesarean section. The most common histological diagnosis was paraovarian-paratubal cysts with the rate of 23.7% (n=9). Cystectomy procedure during the cesarean section did not alter the morbidity of the patient.

Baseret al[50] conducted a retrospective study during the period 2007-2012 on patients who were incidentally diagnosed with adnexal masses while undergoing cesarean section. The patients were surgically managed during cesarean delivery. Clinicopathological characteristics, maternal and neonatal outcomes were assessed. They concluded that, adnexal masses encountered during the cesarean delivery generally have a favorable prognosis in terms of maternal and fetal outcome.

Another retrospective study conducted in France, at Lille University Hospital between 1st January 2007 and 31st December 2010. They found that 12 operations for ovarian masses

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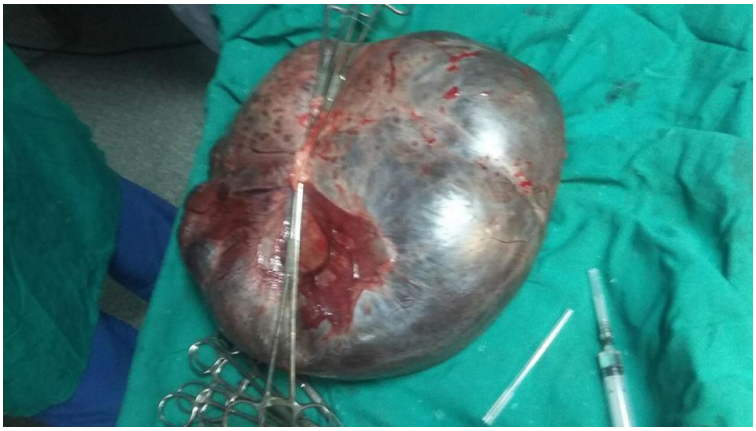
Figure 2: Ovarian Cystectomy during Cesarean Section.



were performed during cesarean section. Operated cysts were most often organic cysts (74.39%). No malignancies were observed, and 3 cases of borderline tumors were diagnosed. There were no obstetrical or neonatal complications (Figure 2).[51]

NON- GYNECOLOGICAL SURGERIES

Intraperitoneal Operations

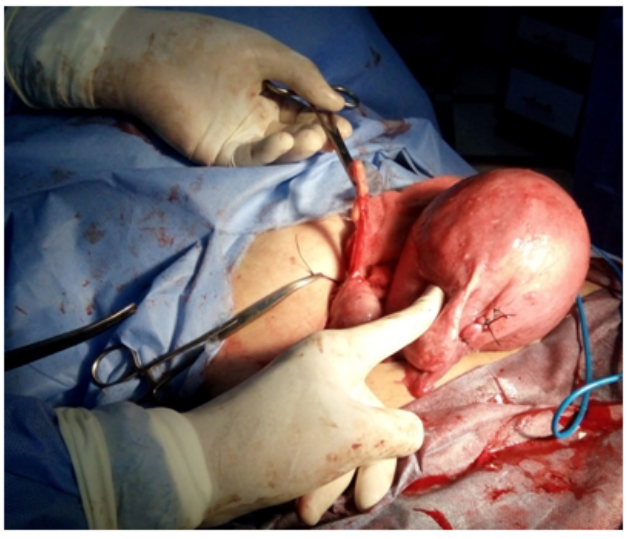
Appendectomy

The incidents of acute appendicitis during pregnancy are approximately 1 in 1500. Acute appendicitis has a non-classical presentation in pregnancy and can occur in the late third trimester. To avoid the risk of future appendicitis occurrence, some surgeons have advocated and performed elective appendectomy at CS (Figure 3) as an acute presentation of this syndrome has a high risk of complications.[52-54]

Continuous spinal anesthesia was developed by facilitate bilateral tubal ligation and appendectomy. Studies have confirmed the safety of performing incidental appendectomy at the time of cesarean section. The authors, therefore, propose that clinicians visualize and palpate the appendix at all cesarean sections, and remove those with evidence of inflammation or disease.[55,56]

Pearce et al[54] performed appendectomy on 93 patients after receiving their written consent to undergo elective cesarean section in a clinic population. The parameters assessed were clinical infection, blood loss, and gastrointestinal tract recovery rates. They found that these parameters were equal in both Groups. Operative time was extended by 15 minutes to the total operation time and the hospital stay was extended by about 12 hours. There were no wound infections or serious morbidity. Prophylactic appendectomy in selected cases, such as women with abnormally appearing appendix, a history of pelvic pain,

Figure 3: Appendectomy and Tubal Sterilization during Cesarean Delivery.



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endometriosis, or anticipated intra-abdominal adhesions do not seem to add to the risk of elective cesarean section.

Systematic reviews were found to support appendectomy or elective appendectomy at cesarean section with no added risks or complications.[57-59]

Extra-Peritoneal Operations

Abdominoplasty

Abdominoplasty is an aesthetic surgical procedure that restores female figure and abdominal contouring. Multiparity and non-pregnancy spacing usually lead to lower abdominal skin redundancy and excess fat accumulation. Moreover, cesarean delivery results in weakness in the lower abdominal wall muscles. Recently, cases of women requesting abdominoplasty at the time of cesarean delivery has soared, since it eliminates the need for another surgery and reduces expenditure. Moreover, gynecologists are learning and upgrading their skills to perform aesthetic surgery, especially abdominoplasty along with cesarean delivery due to the increasing requests from patients.[60]

Ali and Essam[61] conducted a study on 50 pregnant women from 2008 to 2009 who underwent abdominoplasty and limited liposuction at the same time with cesarean section in Kuwait. These cases were compared to 80 cases of abdominoplasty alone. It was found that wound infections, wound dehiscences, and distal skin necrosis were reported more often in women who underwent the combined procedure, than in the ones that underwent abdominoplasty alone. Moreover, the researchers noted that marking the pregnant abdomen was more difficult than the non-pregnant abdomen. Most patients (52%) were not satisfied by the results of combined surgery, where 32% of the patients reported bulging of the abdomen, 24% reported a bulging umbilicus and 12% reported recurrent abdominal skin redundancy. Only 48% of the women were satisfied with the overall results of combined surgery (abdominoplasty with cesarean section). They concluded that, abdominoplasty combined with cesarean delivery carries a higher risk of complications and does not give the desired aesthetic outcome. The authors do not recommend this practice. Thabet et al[62] at Cairo University, Egypt had similar results and conclusions.

Teri et al[60] conducted a review study to evaluate the evidence supporting the results of studies to evaluate abdominoplasty combined with cesarean section. They concluded that the quantity and quality of researches are inadequate and the results of these studies did not recommend a combination of abdominoplasty with cesarean section, as more complications occur, the cosmetic results being unsatisfactory and recurrence being more common.

Hence, concluding from the non-systematic reviews, the application of abdominoplasty combined with cesarean section should be discouraged.

Hernioplasty

Evaluation of the clinical outcome of inguinal or umbilical hernioplasty performed at the time of cesarean section, and comparison of the outcome of this Group with a control population, who underwent a cesarean section alone, was done retrospectively by Gabriele et al.[63] No significant difference was found in the hospital stay, comparing 28 patients with 100 matched controls, who only underwent cesarean section. No complications were recorded during the perinatal and follow-up periods

Chen et al[64] reported the repair of diaphragmatic hernia following the emergency cesarean section, in which they found a part of the transverse colon and a part of omentum trapped in the thorax, through a 3 cm by 3 cm, by laceration in the patient's diaphragm. They removed the trapped intestine which was about 40 cm in length and repaired the diaphragmatic hernia at the same time.

Abdominal wall hernia repair concomitant to cesarean section seems feasible and beneficial to the patient, as the current literature suggests no increased risk in pre or post-operative complications. Moreover, a combined procedure saves the patient from an additional operative procedure.[65]

On the other hand, a high rate of post-operative wound complications were reported, although, comparable to that following a standard elective cesarean section has been observed by some researchers.[66,67]

Evidence supports the combined procedure of cesarean section and hernia repair, thereby concluding that it is feasible and safe.[65]

CONCLUSIONS

Many surgeries could be performed safely in association with cesarean delivery within less time and minimal blood loss. The perspective towards the concept of non-association of other operations with cesarean delivery needs to be changed.

CONFLICTS OF INTEREST

The author has no conflicts of interest.

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Review

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Inclusion of Human Chorionic Gonadotropin in the Family of Therapeutic Glycoproteins

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ABSTRACT

The family of therapeutic glycoproteins contains many members. Some of them have become valuable therapeutic agents in saving the countless number of human lives from some of the most dreadful diseases. They are increasingly taking a center stage among biotherapeutics. The technologies of glycoengineering are making a further impact by modifying the glycan moieties, which make them biologically more active and increase their effectiveness and pharmacokinetics, etc. Human Chorionic Gonadotropin (hCG) has been used in reproductive medicine for the last several decades. The paradigm shift on the hCG actions has created additional therapeutic opportunities against many menacing and dangerous diseases that are no less important than the ones treated by some of the prominent members of the therapeutic glycoproteins family. However, to the best of the authors' knowledge, hCG has never been included in this family or tapped the potential of glycoengineering to make hCG even more therapeutically effective than the currently used preparations. It is time to include hCG in the family and begin glycoengineering on recombinant hormone.

KEYWORDS: Human Chorionic Gonadotropin (hCG); Glycoproteins; Biotherapeutics; Glycosylation.

ABBREVIATIONS: hCG: Human Chorionic Gonadotropin; LH: Luteinizing Hormone; EPO: Erythropoietin; IFNs: Interferons; mAbs: monoclonal antibodies; tPA: tissue plasminogen activator.

HUMAN CHORIONIC GONADOTROPIN

HCG is the hallmark hormone of pregnancy.[1] It belongs to the families of glycoprotein hormones and cystine knot growth factors.[2,3] The glycoprotein hormone family also includes luteinizing hormone (LH), follicle stimulating hormone and thyroid stimulating hormone.[2] They all are heterodimers, consisting of dissimilar, non-covalently bound α and β-subunits.[2] While α subunits are similar, encoded by the same gene, the β-subunits are dissimilar, encoded by different genes.[2] The β-subunit of hCG is encoded by a cluster of six-genes, some of which are pseudogenes.[2] Among the glycoprotein hormones, hCG and LH are not only structurally and conformationally similar, but also bind and activate the same cell surface G-protein coupled receptors.[1,2] The cystine knot growth factors family also includes nerve growth factor, transforming growth factor-β_2, fibroblast growth factor-β and platelet derived growth factor.[3] Even though the family members are structurally unrelated, they share a seat-belt conformation and mediate the pleiotropic actions through binding and activation of the distinct receptors in many different cell systems in the body.

EVOLUTIONARY ASPECTS OF hCG

The genes of hCG β-subunit are evolved from LH β-subunit gene through duplication and mutations, which result in the extension of the c-terminus by about 30 amino acids.[2] The extended part contains additional glycosylation sites.[2] Glycosylation increases the circulatory

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half-life, but it could also have other effects. These hCG features may have aided in the evolution of treetop dwelling primates to protect their pregnancies against all the odds.[4] The receptors and signaling systems must have co-evolved to enable the system operational.[4] Once evolved, the system continued to exist through the present day sub-human primates and humans. It is likely that the hCG evolution may still be continuing. The above presumptive reasoning may explain why hCG has evolved in sub human primates and humans, when they already have a functional homolog LH.

GLYCOSYLATION OF hCG

Glycosylation is a post-translational modification of hCG.[5] It occurs during the translation and processing of hCG subunits in the rough endoplasmic reticulum and Golgi apparatus, by the catalytic action of glycosyl transferases.[5] The process involves the addition of a series of linearly linked and/or branched monosaccharaides.[6] The carbohydrate content accounts for about 30% to 35% of the molecular mass of hCG.[2,5] This amount increases in its hyperglycosylated form, which seems to be present primarily in complicated pregnancies and in trophoblast malignancies.[7,8]

Carbohydrate chains are covalently linked to the protein backbone, either as N-linked at asparagine residues or O-linked units at serine residues.[2,5-7] While α-subunit has 2 N-linked chains, β-subunit has 2 N-linked and 4 O-linked chains.[2,5-7] The Glycosylation differences make hCG a very heterogeneous molecule.[5]

Carbohydrates are not required for the receptor binding of hCG.[2,5,9] However, they are required for the expression of its functions.[2,5,9] The latter comes from its increased survival in the circulation as well as its ability to activate the second messengers' generation at the cell surface.[2,5,9] The removal of carbohydrates increases the receptor binding, but at the same time eliminates hormonal activity of the hCG.[2,5,9] Deglycosylated hCG is an antagonist of glycosylated hCG, because deglycosylated molecule binds receptors, blocking the binding and an activation of the post-receptor signal generation by glycosylated hormone.[2,5,9]

PARADIGM SHIFT ON THE hCG ACTIONS

The only role that hCG was thought to have until about 30 years ago, is the stimulation of corpus luteum secretion of progesterone until about 9th week to maintain pregnancy. Paradoxically, hCG is present throughout pregnancy, albeit at much reduced levels, after the peak levels have been reached at about the 9th week.[1] While the role of hCG in corpus luteum secretion of progesterone during early pregnancy is irrefutable, the old paradigm that believes in hCG having no other functions is not.[1] This is because that there is an incontrovertible evidence for hCG playing multiple roles throughout pregnancy.[1,10]

The hCG actions in non-gonadal tissues can be classified into those that initiate pregnancy, those that favor pregnancy maintenance and finally those that are permissive for the evolution of labor at the end of pregnancy.[1,10,11] These include immunologic tolerance of fetus, behavioral, urodynamic and other changes during pregnancy.[10,11] Instead of showing all the tissues that hCG can regulate, which can be found in the references listed in Table 1, only the relevant tissues to the therapeutic indications are shown.

Table1: Therapeutic opportunities with hCG.[1]

Indication	Tissue	Key actions	References
Breast cancer[2]	Breast epithelial cells	Increase cell differentiation Decrease cell proliferation Decrease metastasis	12,13
Chronic pain[3]	Central nervous system	Neuroplasticity effects Presumed desensitization of central pathways through genetic and non-genetic mechanisms	10,14
HIV/AIDS	Cells of immune system	Release of anti viral cytokine Direct anti-viral effects	15,16
Overactive bladder	Detrusor muscle	Inhibition of contractions	17
Painful bladder/interstitial cystitis	Urothelium	Repair and/or replace the damaged urothelial cells	18
Pre-term birth[4]	Myometrial smooth muscle	Inhibition of contractions	19
Rheumatoid arthritis, Sjogren's Syndrome and the other autoimmune diseases that ameliorate during pregnancy.[5]	Cells of immune system	Direct effects on the cells of immune system Modulation of theircytokine secretion	20
Tubal infection with Nesisseria Gonorrhoeae	Tubal epithelial cells	Inhibition of molecular mimicry mechanism used by the pathogen	21

[1]May also include therapies for injury and inflammation of other target tissues including, central and peripheral nervous systems.
[2]Includes decreasing the breast cancer risk in young women, who plan to delay their first childbirth.
[3]Includes chronic pain due to many different conditions.
[4]May also include several other pregnancy complications.
[5]Lupus erythematosus; type 1 diabetes; ankylosing spondylitis; multiple sclerosis; thyroiditis; Crohn disease; Hepatitis.

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Multiple Exciting New Therapeutic Opportunities with hCG

The studies on non-gonadal actions of hCG have yielded greater number of therapeutic opportunities than those on the gonadal actions. These opportunities may seem far-fetched, but they are not, as amply discussed in the references cited in Table 1. The table shows the list along with the relevant tissues and key actions. Instead of reiterating the details, which are a part of articles cited in the table, general discussion that applies to all of the therapies has been provided. Admittedly, there are still many lacunae and these knowledge gaps can only be filled by further research.

Many of the illnesses in Table 1 can be fatal. All of them can have long-lasting troublesome effects, debilitating, come with chronic pain and suffering, sleep deprivation, depression, anxiety, social isolation and stigma, loss of sexual intimacy, productivity in the work place, job and health insurance, etc. The family members and friends of affected individuals often face emotional problems and economic setbacks. The cost to the U.S. economy alone runs into millions to billions of health care dollars per year.

There are current therapies for these illnesses, but they are not either effective or come with severe side effects. Many are quite expensive and a few have a low tolerability. There is clearly an unmet need for the cost effective and safer therapies. hCG therapy could be one of them and it will be relatively safe and cost effective. Judging from anecdotal evidence, studies on animal models, cells and tissues and on human subjects in some cases, hCG therapy is likely to work for these diseases. To realize this promise, randomized, double-blinded, placebo controlled clinical trials have to be performed with optimal hCG doses, route and frequency of administration and an appropriate selection of the patients. These may vary with the disease.

The cost of clinical trials can exceed 50 to 100 million dollars. The cost comes with an expectation that the trials show benefits. From the evidence that hCG treatments are likely to work, financial rewards can outweigh the financial risks.

The hCG therapies will have a minor to tolerable side effects as compared with many of the current therapies. The effectiveness can be further enhanced by newer technologies, which do exist and can be made to work for hCG. The important one will be making "hCG Pills", using the procedures that are being employed for developing insulin pills.[12] This technology permits encapsulating hCG in spheres of neutral lipid molecules, that insulates hCG from destruction by stomach acids. The availability of pill will have a huge impact on the hCG use even in the remote areas of the world.

Orally active LH agonists, that can induce ovulation, are already available.[13,14] However, it is not known whether they will be comparable to hCG pills. In support of the possibility that they could be different are the findings that showed LH and hCG are not completely functionally equivalent and they may not activate the same genes or to the same extent.[15] Thus, the therapeutic benefits that hCG pills offer may not necessarily be the same as oral LH agonists.

The effectiveness of hCG can also be increased by well planned combination therapies. They could lower the toxicity of currently used drugs; reduce the cost, while preserving their desirable properties. Moreover, the combination therapies can be more active than single therapies because of the differences in their mechanisms of action. The potential hCG therapies should not be considered as panacea and they may not completely replace the current therapies. Instead, they can complement them and become an important part of physician's toolbox to treat these diseases. So what do we lose by exploring them?

Inclusion of hCG in the Family of Therapeutic Glycoproteins

The family of therapeutic glycoproteins contains many members.[16,17] While living cell systems can make many of them, others can be made by glycoengineering. Some of them are already in clinical use, saving countless number of human lives. Many others are in clinical trials. Currently therapeutic glycoproteins account for more than one-third of the U.S. Food and Drug Administration (FDA) approved biotherapeutics and this number is likely to increase rapidly in the near future. They are made in eukaryotic systems and marketed under various trade names.

The members of the family come from different sources and vary in the amount of glycan moieties, their sizes, structures, amino acid composition, conformation, folding patterns, etc.[16,17] Among the family members, four are selected for brief discussion to highlight their importance in the treatment of some of the most dreadful human diseases. The four are, erythropoietin (EPO), interferons (IFNs), monoclonal antibodies (mAbs) and tissue plasminogen activator (tPA).

EPO is a glycoprotein hormone primarily made by kidneys in adults and by liver in fetus and neonates.[18,19] It is highly glycosylated (40%) and produced in response to hypoxia. It controls the production of red blood cells (RBC) through its cytokine like actions on their precursors in the bone marrow.[18,19] It is used for the treatment of anemia due to chronic kidney disease, chemotherapy and radiation treatment for cancers, myelodysplasia, inflammatory bowel disease and ulcerative colitis.[18,19]

IFN are a group of proteins that are made by virus (or other pathogens) infected cells in the body.[20,21] They belong to cytokine class family, which are communication molecules to trigger the protective defenses of the immune system.[20,21] There are 3 types; IFN-β belongs to type 1 and IFN-γ to type 11.[20,21] Among the IFNs, β and Y are glycoproteins.[20,21] They are antiviral molecules and can modulate the functions of immune system.[20,21] They are used for the treatment of chronic granulomatous disease and multiple sclerosis.[20,21]

mAbs are produced by hybridoma technology and contain 2 heavy and 2 light chains covalently bound by disulfide bridges.[22,23] Five of the top 10 best selling pharmaceutical prod-

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ucts in 2016 are mAbs. The FDA approved the use of about 30 of them and more than 200 others are currently under clinical trials.[24,25] They bind monospecifically to the cell surface antigens of cancer and other cells and trigger the events that culminate in their death.[26,27] The immunotherapies against cancers and some autoimmune diseases with mAbs are rapidly gaining ground.[28,29]

tPA is a serine protease made by vascular endothelial cells.[30,31] It breaks down the blood clots *via* the plasmin generation.[30,31] It is the standard of care for the treatment for acute ischemic strokes.[32,33] It is most effective when it is used within 3 to 4.5 hrs after the first onset of symptoms.[32,33] It is also used for the treatment of pulmonary embolism and myocardial infarctions, which are associated with blood clots.[34,35]

hCG has been used for the past several decades for the induction of follicular maturation and ovulation and for the treatment of hypogonadotropic hypogonadism in males. It is becoming increasingly clear from the studies on non-gonadal actions that hCG has rather a broad therapeutic potential against many diseases, that are no less devastating than the ones treated by EPO, IFNs, mAb and tPA. However, it has never been included in the family of therapeutic glycoproteins. Such inclusions can fast track glycoengineering research on hCG to make it therapeutically more effective than the currently used preparations.

There has been a declining interest among biotechnology and pharmacy companies to invest resources in the further development of hCG analogs. This is due to smaller market share for them as compared with the demand for agents to treat cancers and autoimmune diseases. The declining interest could reverse, once the companies come to grips with the multiple hCG therapies.

Glycoengineering

Glycoengineering consists of series of technologies that allow modifying the quantity as well as the quality of the existing glycan moieties in the glycoproteins.[36,37] It can also add glycan moieties to non-glycoproteins. The modifications include changing the total amount of carbohydrate, linear or branching pattern, monosaccharaides composition or even adding new chains at different sites on the protein back bone. These changes could further increase the circulatory half-life and also can improve the molecular stability, protect against proteolytic degradation, oxidation, chemical cross linking, pH denaturation, and aggregation and increase the solubility.[37-40] All these desirable features can increase the effectiveness and pharmacodynamics of therapeutic glycoproteins.[36] Thus, glycoengineering is becoming a valuable tool in the production of safe and effective therapeutic glycoproteins. It is also helping with minimizing some of the pharmaceutical problems and enhancing the production of safe and high quality products. However, many challenges still remain.

To the authors' knowledge, glycoengineering has never been used to increase the therapeutic effectiveness of hCG. It is now time to do so because of the multiple exciting new therapeutic opportunities with hCG (Table 1). However, it is not known what glycan changes are necessary to make hCG more effective than the natural product. Moreover, the optimal changes could vary with the clinical indication. Thus, a great deal of work is needed.[41-43]

CONCLUSION

Even though, recombinant hCG is commercially available, urine derived hormone is often used in reproductive medicine. Batch-to-batch variations in urine derived hCG are known to exist and they could be coming from carbohydrate heterogeneity due to the isolation and purification procedures. Therefore, we recommend using recombinant hCG for glycoengineering, as it is likely to ensure the production of a consistent and high quality homogeneous products. Once glycoengineered hCG is made, it could be used in making the hCG pills. The availability of glycoengineered hCG in a pill form could lead to an world-wide expansion of its use.

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