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Project Title: Prediction of pregnancy outcomes through hCG alone in women presenting with vaginal bleeding in early pregnancy

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Summary (250 words max single spaced):
Introduction: Women experiencing vaginal bleeding in early pregnancy are managed based on serum concentration of human chorionic gonadotropin (hCG) and pelvic ultrasonography. Despite the robust data on using serial hCG values, there is a lack of data on the utility of a single initial hCG value in predicting pregnancy outcomes.
Methods: Several aspects of the relationship between a single initial hCG and pregnancy outcome were evaluated using a cohort of patients seen at the Winnipeg Health Sciences Centre (HSC) Early Pregnancy Assessment Clinic (EPAC) (n=3266).
Results: Human chorionic gonadotropin alone is an excellent marker of viability (hCG cutoff = 16,134 IU/L, area under the curve (AUC) = 0.9173) and a fair marker for ectopic pregnancy (hCG cutoff = 2,052 IU/L, AUC = 0.7885). Patients presenting with hCG values 263-489 IU/L are at the highest risk of a final diagnosis of ectopic pregnancy and ectopic pregnancy can be considered highly unlikely when hCG >40,000 IU/L. The combined diagnoses of early pregnancy failure and incomplete abortion form the majority of initial diagnoses between roughly 3,500-22,000 IU/L and patients in this range may be told to attend EPAC fasting as to allow for same day surgical management. Diagrams created represent a novel method to denote probability of various pregnancy outcomes at a single initial hCG and may aid to risk stratify as well as counsel patients.
Conclusion: A single initial hCG alone may be used to predict viable pregnancy and prioritize women presenting with vaginal bleeding in early pregnancy requiring urgent ultrasound.

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Introduction and Background

Women experiencing vaginal bleeding in early pregnancy are diagnosed and managed based on serum concentration of human chorionic gonadotropin (hCG) and pelvic ultrasonography. The employment of such testing has permitted the timely detection of pregnancy and has substantially decreased the complications associated with ectopic pregnancy.[1,2] Patients presenting to the emergency department with bleeding in early pregnancy often have access to rapid hCG results, but have to wait for daytime weekday hours to receive an ultrasound. Therefore, there exists a need for accurate diagnoses in women experiencing vaginal bleeding in early pregnancy in order to prevent potentially life-threatening outcomes without compromising viable pregnancies.

Human chorionic gonadotropin begins to rise 8 days following ovulation and may be abnormally low in patients with an ectopic pregnancy or threatened abortion and abnormally high in patients with trophoblastic disease.[3] In a non-symptomatic viable pregnancy, hCG levels continue to increase to a peak of roughly 100,000 IU/L at 10 weeks gestation and subsequently decrease to a stable value of roughly 20,000 IU/L.[4,5] For patients receiving an ultrasound, an hCG level >1,500 IU/L is likely to receive an accurate diagnosis.[6] A number of techniques are currently applied in practice utilizing the rise in hCG to distinguish a viable pregnancy from a nonviable pregnancy. In symptomatic patients, a viable intrauterine pregnancy is expected to demonstrate a minimum 24% rise in hCG at 1 day and a 53% rise in hCG at 2 days.[4] Moreover, patients with ectopic pregnancies may demonstrate an abnormal hCG doubling time, while those with pregnancy failures may demonstrate declining hCGs.[7] Ectopic pregnancies are particularly difficult to diagnose as patients may initially present with high or increasing hCG values similar to viable pregnancy, declining or low hCG values similar to pregnancy losses or plateauing hCG values.[7–10] Despite the robust data available on using serial hCG values,[4,7,11] there is a clear lack of data available on the utility of a single hCG value in predicting pregnancy outcomes.

The purpose of this research is to evaluate the prediction capabilities of a single initial hCG value for pregnancy outcomes in stable outpatients <14 weeks gestational age with vaginal bleeding with or without pelvic pain. Several aspects of the relationship between initial hCG and pregnancy outcome will be evaluated using groups derived from patients seen at the Winnipeg Health Sciences Centre (HSC) Early Pregnancy Assessment Clinic (EPAC). An initial ultrasound diagnosis group will be created to examine multiple aspects of the relationship between hCG and initial pregnancy outcomes of viable pregnancy, ectopic pregnancy, early pregnancy failure, incomplete abortion, and pregnancy of unknown location (PUL). A final diagnosis group will be created to evaluate the relationship between initial hCG and final pregnancy outcomes of viable pregnancy, pregnancy loss, and likely ectopic pregnancy. Further evaluation of final pregnancy outcomes and initial hCG in patients with an initial ultrasound diagnosis of intrauterine pregnancy (IUP) of uncertain viability or PUL will also be performed.

These results will aid Emergency Department, and primary care health care providers and Obstetricians in counseling symptomatic patients less than 14 weeks pregnant on their hCG values alone and the corresponding likelihood of viable pregnancy, pregnancy loss and ectopic pregnancy. This study will also provide better data on the likelihood of an accurate diagnosis when an ultrasound is performed within 72 hours of an hCG for women with vaginal bleeding in the first trimester of pregnancy. It will also aid clinicians to better predict the relationship between initial hCG and final pregnancy outcomes in patients initially diagnosed with an IUP of uncertain viability or PUL. As such, clinicians can approach cases with this understanding and better prioritize those requiring urgent ultrasound testing.

Materials and Methods

A retrospective study of 3266 patients seen at the Winnipeg Health Sciences Centre (HSC) Early Pregnancy Assessment Clinic (EPAC) between January 23, 2006 and December 31, 2012 was performed. The majority of patients were referred from the HSC Emergency Department, while others were referred from Obstetricians, or other Emergency Departments. Patients eligible for inclusion were pregnant women less than 14 weeks gestational age experiencing vaginal bleeding with or without pelvic pain who had an initial hCG value between 5 and 350,000 IU/L. Human chorionic gonadotropin values taken at HSC were provided by Diagnostic Services of Manitoba Clinical Biochemistry & Genetics using an assay that detects both the beta subunit alone and the intact molecule (Roche Diagnostics). Precision coefficient of variation values were as follows: 4.4-4.6% for mean hCG 4.81 IU/L, 1.3-2.6% for mean hCG 880 IU/L, and 1.7-3.1% for mean hCG 7949 IU/L. Once in EPAC, a focused history and physical was performed with or without the completion of an ultrasonographic assessment using transvaginal and/or abdominal probes (Biosound Esaote Picus III system). Subsequent serum hCGs or ultrasonographic assessments were performed as necessary until a final diagnosis was reached, the patient chose to follow up with their own physician or the patient was lost to follow up.

Validation of hCG values was completed through the HSC Attachmate electronic system or physical reports in patient records and ultrasound assessments were attained directly from EPAC patient records or previously completed database entries. When exact times were unavailable, EPAC visits were listed as 08:00 h as all patients referred to EPAC are told to attend at this time and EPAC ultrasound diagnoses were listed as 09:00 h. Furthermore, the time for ultrasound diagnoses outside of EPAC, hCG values not included in HSC Attachmate or any surgery were listed as 12:00 h by convention. Standard nomenclature for pregnancy diagnoses and diagnoses of Pregnancy of Unknown Location (PUL) outcomes were followed where available and are included in Tables 1 and 2.[1,11–13] This study was approved as written by both the Delegated Review Board of the University of Manitoba Health Research Ethics Board and the Health Sciences Centre Research Impact Committee (Prediction of pregnancy outcomes through hCG alone in women presenting with bleeding in early pregnancy, #HS19618 (H2016:135)).

The initial ultrasound diagnosis group was used to examine the relationship between initial hCG and the first ultrasound performed either 72 hours after the initial hCG or the hCG taken up to 24 hours after the first ultrasound. Beginning with all EPAC patients (n=3266), 181 patients that lacked an hCG value and 26 patients with an hCG value less than 5 IU/L were removed. Next, 16 patients were removed that were referred by their obstetrician to EPAC solely to receive intramuscular methotrexate and 1 patient was removed as they did not attend EPAC. One patient was removed due to their initial referral for retained products after a therapeutic abortion and 5 patients were removed for inadequate records of their diagnoses. Next, 13 patients with an initial ultrasound performed more than 24 hours before their initial hCG were removed and 178 patients with no initial ultrasound available were removed. Then 152 patients with an initial ultrasound performed more than 72 hours after their initial hCG were removed. Then, 1 patient with an incorrect diagnosis, another patient that took misoprostol without consulting a physician, and 5 patients with diagnoses of a viable pregnancy >14 weeks gestational age were excluded. Lastly, 3 patients were removed as their initial hCG exceeded 350,000 IU/L. Thus, 2683 patients were labeled as the initial ultrasound diagnosis group and were included in examining the relationship between initial hCG and initial ultrasound diagnosis of viable pregnancy, ectopic pregnancy, early pregnancy failure, incomplete abortion and PUL.

Receiver Operating Characteristic (ROC) analyses were performed to determine the ideal hCG level to make initial ultrasound diagnoses. Additional analysis using a statistical diagnostic test examined the sensitivity, specificity, PPV and NPV of initial hCG values for the initial diagnosis of

viable pregnancy. A graphical analysis was performed using the first 2600 patients ordered by ascending hCG and stratified further into groupings of 100 patients i.e. 1-100, 101-200, etc. These groupings of 100 were analyzed for the range of hCG values and cases of initial diagnoses of PULs, ectopic pregnancies (including definite and probable ectopic pregnancy), viable pregnancies alone, early pregnancy failures alone, as well as those eligible for dilation & curettage (including early pregnancy failure and incomplete abortion). The plot was constructed using only the maximum hCG value and the percentage of the initial ultrasound diagnoses previously stated in each grouping of 100 patients. Of note, total percentages at a given maximum hCG value will amount to less than 100% since molar pregnancies and complete abortions were not shown as they were unrelated to the research question and/or represented a small proportion of diagnoses.

The final diagnosis group was used to evaluate the relationship between initial hCG and final diagnosis of viable pregnancy, intrauterine pregnancy loss, and ectopic pregnancy using the following exclusion criteria. Beginning with 3266 patients, 181 patients were removed as they did not have an hCG value and 26 patients were removed as they had an initial hCG value less than 5 IU/L. Then, 16 patients were removed as they were referred to EPAC solely to receive intramuscular methotrexate and were followed by their own obstetrician. Five patients were removed for insufficient records of diagnoses and 1 patient was removed for not attending. Next, 1 patient with retained products after a therapeutic abortion and 1 that consumed misoprostol without consulting a physician were excluded. Five patients were removed as their pregnancy was determined to be >14 weeks gestational age. Then patients with an initial diagnosis of PUL or IUP of uncertain viability with no further record in EPAC were excluded due to a lack of a definitive final diagnosis; these accounted for 33 and 46 patients respectively. Ten Patients were then removed for lacking an initial hCG value time and 3 patients were removed for an initial hCG >350,000 IU/L. Patients with an initial hCG taken greater than 96 hours before their initial presentation to EPAC or who received an initial hCG more than 24 hours after their initial presentation to EPAC were excluded. This resulted in the exclusion of 89 and 11 patients respectively. Thus, 2838 patients were labeled as the final diagnosis group and were included in analyzing the relationship between initial hCG and final diagnosis. The same analyses performed for the initial ultrasound diagnosis group was used for the final diagnosis group. The categories for graphical analysis included viable pregnancy alone, intrauterine pregnancy loss (including CA, EPF, HIUP, IA, SRP, SASR, PULAD, PULID, PULRP, PULSR, and PULTP receiving vaginal misoprostol), and ectopic pregnancy (including DEP, ECT, HEP, PE, SPE, PULTP, and TPE), see Tables 1 and 2 for abbreviations.

The IUP of uncertain viability (IUV) group was created to examine the final outcomes of patients initially diagnosed with an IUV. Beginning with the initial ultrasound diagnosis group (n=2683) specified above, all non-IUV initial diagnoses were excluded resulting in the removal of 2436 patients. Next, cases of molar pregnancy were removed (n=2) due to their small numbers and lack of relevance to the research question. Then 33 patients were removed, as they did not have final outcome data available. Lastly, 1 patient was removed, as the initial diagnosis of IUV was an error and the pregnancy was later determined to be ectopic. Patients were then grouped into either viable pregnancy or IUP loss. Thus, 211 IUV patients labeled IUV group were analyzed using survival analysis for the relationship between initial hCG and final diagnosis of viable pregnancy.

A PUL group was formed to investigate the final outcomes of patients initially diagnosed with a PUL. Starting with the initial ultrasound diagnosis group (n= 2683), all non-PUL initial diagnoses (n=1919) as well as any final diagnosis of molar pregnancy (n=2) were excluded as they did not fit the research question. Thirty-five patients were subsequently removed for lacking final

outcome data, 27 had a diagnosis of PUL on their last ultrasound while 8 were IUP of uncertain viability. The final outcomes were grouped into viable pregnancy, ectopic pregnancy, and intrauterine pregnancy loss. Hence, 727 patients were labeled PUL group and evaluated with survival analysis for the relationship between initial hCG and final diagnosis of viable pregnancy or ectopic pregnancy was performed.

Interpretation of results
The following computed Area Under the Curve (AUC) values will be used to determine the accuracy of ROC analyses: excellent (AUC 0.9-1), good (AUC 0.8-0.9), fair (AUC 0.7-0.8), poor (AUC 0.6-0.7), fail (AUC <0.6). The survival analyses utilized p-values and hazard ratios with a 95% confidence interval (CI). A significant p-value was defined as $p<0.05$. A hazard ratio <1 indicates a decrease in probability for the outcome being examined when hCG increases compared to controls while a hazard ratio >1 denotes an increased probability of the outcome when hCG increases.

Results
All groups were derived from all EPAC patients (n=3266) seen between January 23, 2006 and December 31, 2012 using specified exclusion criteria and are described in Table 3. Although these groups are described separately, most had significant overlap in patients due to similar exclusion criteria.

Viable Pregnancy
The ROC analysis performed on the initial ultrasound diagnosis group (n=2683) to distinguish an initial diagnosis of viable pregnancy (n=1001) from any other initial pregnancy diagnosis determined the ideal initial hCG to be 17,942 IU/L with a sensitivity of 0.909, specificity of 0.914 and AUC of 0.9661. The ROC analysis performed on the final diagnosis group (n=2838) for the final diagnosis of viable pregnancy (n=1186) determined the ideal initial hCG cutoff to be 16,134 IU/L with a sensitivity = 0.852, specificity = 0.893, and AUC = 0.9173. The survival analysis for IUPs of uncertain viability (n=211) compared the outcomes of viable pregnancy (n=83) and used IUP losses (n=128) as controls. The p-value for this analysis is significant at 0.0315 with a hazard ratio = 1.756 and 95% CI = 1.051 - 2.932 which indicates as hCG value increases, the probability of viable pregnancy increases. Viable pregnancies represented 39% of final diagnoses in patients initially diagnosed with an IUP of uncertain viability. The survival analysis utilizing the PUL group (n=727) was insignificant for the final outcome of viable pregnancy (n=53), hazard ratio = 1.198 (95% CI 0.886-1.622), p-value = 0.2409 and viable pregnancy represented 7% of final diagnoses while spontaneously resolving PUL represented 61% of final diagnoses. The PUL group had a mean hCG of 2,459 IU/L and range 5-57,473 IU/L.

While graphs displaying the results of the statistical diagnostic test for sensitivity, specificity, PPV, and NPV of a given hCG for the initial and final diagnosis of viable pregnancy were created, trends were similar and as such only the final diagnosis group was included. Figure 1 represents a graphical depiction of this abbreviated data and includes hCG values ≤136,707 IU/L due to the small sample size above this hCG value. Figure 1 demonstrates that as expected, larger hCG values are associated with higher specificity and to an extent PPV for diagnosing a viable pregnancy. The variation in PPV when hCG >150,000 IU/L (data not shown) likely arises from cases of molar pregnancy and the small number of EPAC patients with hCGs reaching these values. For example, in the initial ultrasound diagnosis group there were roughly 80 patients with hCG values above 136,707 IU/L, 5 of which had molar pregnancies, 1 had an early pregnancy failure and the remainder were viable. Furthermore, elevated hCG values are also associated with a lower sensitivity and NPV for diagnosing a viable pregnancy. Various graphs were created to account for patients presenting with hCG values not amenable to using the

previously described ROC analyses. Figures 2 and 3 reinforces that viable pregnancies are more likely at high hCG values. Figure 2 demonstrates that viable pregnancies represent approximately 60% of initial diagnoses at an hCG range of 22,695-29,622 IU/L and continue to increase to approximately 90% of initial diagnoses at an hCG range of 45,857-54,421 IU/L. Figure 3 demonstrates that viable pregnancies represent roughly 90% of final diagnoses when hCG ranges from 46,479 to 54,406 IU/L.

Ectopic Pregnancy

The initial diagnosis (n=2683) of ectopic pregnancy (n=69) ROC analysis revealed an initial hCG of 3,096 IU/L with a sensitivity of 0.638, specificity 0.689 and AUC of 0.7277. The ROC analysis for the final diagnosis (n=2838) of ectopic pregnancy (n=155) demonstrates an ideal initial hCG of 2,052 IU/L with sensitivity = 0.703, specificity = 0.758, AUC = 0.7885 - fair. When the optimal hCG cutoff of 2,052 IU/L is applied to the final diagnosis group, 110 ectopic pregnancies of the total 155 cases would be diagnosed while 45 cases would be missed. The survival analysis utilizing the PUL group (n=727) was insignificant for the final outcome of ectopic pregnancy, hazard ratio = 0.961 (95% CI 0.750-1.233), p-value = 0.7564 and ectopic pregnancy represented 11% of final diagnoses. Several graphs describing the relationship between hCG and ectopic pregnancy were generated (Figures 2-4). Figure 2 determines the risk of initially diagnosing an ectopic pregnancy to be as high as 8% between an hCG range of 369-630 IU/L, while Figures 3 and 4 demonstrate that the risk of a final diagnosis of ectopic pregnancy is as high as 22% between an hCG range of 263-489 IU/L. When ordered by ascending hCG value, the last initial ultrasound diagnosis of ectopic pregnancy was seen at an hCG of 38,232 IU/L and represented a definite ectopic pregnancy. Additionally, the last 2 cases of ectopic pregnancy in the final diagnosis group were seen at an hCG range of 31,392-38,564 IU/L (Figure 3).

Intrauterine Pregnancy Loss

Early pregnancy failure (EPF) as an initial diagnosis displayed an unsatisfactory AUC of 0.5684 and initial diagnosis of pregnancy loss excluding EPF (including CA, DEP, IA, MP, and PE) displayed a poor AUC of 0.6506 (results not shown). The ideal initial hCG to make a final diagnosis of an intrauterine pregnancy loss is 14,019 IU/L with a sensitivity = 0.87, specificity = 0.775, and AUC = 0.8544 - good. Various graphs illustrating the relationship between hCG and initial diagnosis of early pregnancy failure (Figure 2) or final diagnosis of intrauterine pregnancy loss (Figures 3 and 4) are included in this report. The risk of early pregnancy failure as an initial diagnosis increases steadily until reaching a peak of 45% when initial hCG is between 7,901 and 9,551 IU/L (Figure 2). The oscillation of intrauterine pregnancy losses as a final diagnosis (Figure 3 and 4) when maximum hCG <1,200 IU/L is likely due to the peak in ectopic pregnancies while the oscillation between maximum hCG values of roughly 3,000-5,500 IU/L is likely due to both viable pregnancies and ectopic pregnancies. The combined group of incomplete abortions and early pregnancy failures represent the majority of diagnoses between hCG data points of 3,445-4,218 IU/L and 16,489-22,676 IU/L. The junction between viable pregnancy and intrauterine pregnancy loss occurs between hCG values of 16,489 to 22,676 IU/L; after which percentage of final diagnosis values continue trending upwards for viable pregnancy and downwards for intrauterine pregnancy loss (Figure 3).

Discussion

Viable Pregnancy

The ROC analysis performed demonstrates a single initial hCG is an excellent test to separate initial diagnosis of viable pregnancy as well as final diagnosis of viable pregnancy. An hCG of 16,134 IU/L and 17,942 IU/L must be reached respectively, to assume this relationship. The percentage of final diagnoses of viable pregnancy was 42% and is lower than the available literature value of 49.3% in symptomatic women.[14] The majority of women experiencing vaginal

bleeding in early pregnancy are concerned about the viability of their pregnancy and may find any quantitative information valuable. As such, these tools may help inform discussions with symptomatic patients regarding the probability of viable pregnancy using hCG alone.

In cases initially diagnosed with an IUP of uncertain viability, as initial hCG increases, the probability of viable pregnancy increases as compared to IUP losses (p=0.0315). Current literature lists viable pregnancies as representing 44% of outcomes at 11-14 weeks gestation in patients initially diagnosed with an IUP of uncertain viability and is congruent with the 39% reported in this study.[18] These results suggest women initially diagnosed with an IUP of uncertain viability could conceivably be advised of the high risk of pregnancy loss overall and the increased probability of viable pregnancies as the average hCG increases. Cases initially diagnosed with PUL demonstrated insignificant p-values with survival analysis, however, hazard ratios trended towards higher hCG values developing into viable pregnancies. The large variation in hCG in the PUL group may be explained by very recently expelled pregnancies for which hCG has not had sufficient time to decrease.

Ectopic Pregnancy

Initial hCG is fair in distinguishing the initial diagnosis of ectopic pregnancy (AUC=0.7277) from a non-ectopic pregnancy when an ideal hCG of 3,096 IU/L is attained. The ability of initial hCG to distinguish ectopic pregnancies from non-ectopic pregnancies is slightly increased when regarded as a final diagnosis (AUC=0.7885) and utilizes a lower initial hCG threshold of 2,052 IU/L. Ectopic pregnancies represented 5.5% of all outcomes in the final diagnosis group and is reflective of currently available literature citing ectopic pregnancy risk as 2.3-7% in women presenting to a clinic similar to EPAC.[15] Cases initially diagnosed with PUL demonstrated insignificant p-values with survival analysis, however, hazard ratios trended towards lower hCG values resulting in ectopic pregnancies. While this data found ectopic pregnancies to represent 11% of final diagnoses in patients initially presenting with PUL, available data from a clinic similar to EPAC determined this number to be 6.8%.[15] The discrepancy may arise from the lower median hCG in this study's PUL group of 786 IU/L as compared to 2,273 IU/L.[15] Furthermore, this dataset consisted of minimal self-referred patients (<1%), while the comparison clinic cited freely accepted self-referred patients potentially leading to a dilution of ectopic pregnancy outcomes.[15]

The trends exhibited by the ectopic pregnancy cases in graphs are also reflected in the literature.[16,17] An initial or final diagnosis of ectopic pregnancy is exceedingly unlikely at an initial hCG of >40,000 IU/L (Figure 2 and 3) and is in line with current research suggesting an optimal hCG cutoff of 40,000 IU/L to exclude ectopic pregnancy.[16] In combination, Figures 3 and 4 are consistent with available data regarding the higher likelihood of ectopic pregnancy in patients presenting with vaginal bleeding with or without pelvic pain when hCG <1,500 IU/L.[17] Given the potential for life-threatening sequelae with ectopic pregnancies and merely fair study results, this study does not support the use of a single hCG alone to make either an initial or final diagnosis of ectopic pregnancy. It may, however, help to stratify the risk of ectopic pregnancy and aid in determining which patients require an urgent ultrasound. This is in line with other available ectopic pregnancy research that recommends serial hCG values and/or urgent ultrasonography when ectopic pregnancy is suspected.[1,8]

Intrauterine Pregnancy Loss

Initial hCG is an unsuitable discriminator between outcomes in categories of early pregnancy failure (AUC=0.5684) as well as a poor discriminator of pregnancy loss excluding early pregnancy failure (AUC=0.6506) (data not shown). Initial hCG of 14,019 IU/L is a good discriminator between a final diagnosis intrauterine pregnancy losses (AUC=0.8544) and other

pregnancy outcomes. In combination with Figures 2-4, these tools can be used to inform discussions with patients regarding their likelihood of pregnancy loss at various hCG values. Additionally, it may be advisable for physicians referring patients to EPAC with an hCG of roughly 3,500-22,000 IU/L to attend EPAC fasting as early pregnancy failures and incomplete abortions form the majority of initial pregnancy diagnoses in this hCG range (Figure 2). Fasting patients with these diagnoses are able to undergo same day dilation and curettage and potentially benefit from earlier resolution of bleeding.

Limitations

While the results of this study are promising for the use of a single hCG value in predicting pregnancy outcomes in women presenting with vaginal bleeding in early pregnancy, there are several limitations. This data did not account for errors in laboratory initial hCG values as it did not utilize repeated hCG values directly in analyses. Additionally, factors that may affect hCG including pain or cramping (possible increase in uterine clearance resulting in lower hCG values)[11], gestational age[4,5] and patient age[11] were not corrected for in this study. Moreover, any vaginal bleeding in early pregnancy was sufficient for inclusion and stratification in terms of quantity (spotting, presence of clots, etc.) was not accounted for. Data collected on vaginal bleeding and pain before presentation was dependent on a self-described patient history and as such is subject to recall bias. Furthermore, this study may also be subject to self-selection bias as it only captures the patients who present for medical attention with vaginal bleeding in early pregnancy. Bias may also arise from this study's ability to examine outcomes in patients solely during their EPAC appointments as in the majority of cases the data did not account for diagnoses made after EPAC determined the follow up to be complete and excluded those without final diagnoses lost to follow up (n=79). Figures 2-4 had multiple distinct ranges of hCG values for which percentage of initial and final diagnoses were known. These scatter plots utilized only the maximum hCG and were connected for ease of use. It should be noted that values between maximum hCG values represent an extrapolation of the known relationship. As with any retrospective study, some records were missing or incomplete and may have affected diagnoses in the data set for a few patients. Variation in ultrasonographer ability and equipment amongst individual obstetricians as well as radiologists were not accounted for as they are limitations inherent to clinical practice. Lastly, this data was collected in clinically stable outpatients and as such may not apply appropriately to women requiring inpatient management.

Future Directions

The relationship between hCG and time to final diagnosis or number of EPAC visits required to reach a final diagnosis were not examined in this study and may pose an interesting research question. In conjunction with the current study, this new information may help in counseling women with bleeding in early pregnancy on likelihood of pregnancy outcomes and expected timeframes for definitive diagnoses. An additional research question could evaluate the relationship between hCG and success of treatment options selected by the patient (using expectant management as control) as well as time to receiving treatment. These treatment options include dilation & curettage or misoprostol for early pregnancy failure and incomplete abortion; methotrexate, salpingectomy or salpingostomy for ectopic pregnancy; and methotrexate or dilation & curettage for persisting PUL. Another possible research question could assess the relationship between quantity of vaginal bleeding as well as the presence of clots or pelvic pain and pregnancy outcomes. Finally, future studies should account for the gestational age of the pregnancy as it was a major limitation of this research.

Conclusion

In women presenting with vaginal bleeding with or without pelvic pain in early pregnancy, hCG alone is an excellent marker of viability and viable pregnancies form roughly 90% of final

diagnoses when hCG ranges from 46,479 to 54,406 IU/L. Patients presenting with hCG values 263-489 IU/L are at the highest risk of a final diagnosis of ectopic pregnancy and ectopic pregnancy cannot be deemed unlikely until an hCG >40,000 IU/L is reached. Physicians may use the tools in this study for risk stratification, however, due to possibility for life-threatening sequelae, the diagnosis of ectopic pregnancy should remain dependent on repeat hCG and/or urgent ultrasonography. Intrauterine pregnancy loss becomes less likely than viable pregnancy as a final diagnosis between hCG values of 16,489 to 22,676 IU/L IU/L and may be used in counseling patients on their risk of pregnancy loss. The combined diagnoses of early pregnancy failure and incomplete abortion form the majority of initial diagnoses between roughly 3,500-22,000 IU/L and patients in this range may be told to attend EPAC fasting as to allow for same day management with dilation & curettage. A single initial hCG alone may be used to predict viable pregnancy and prioritize women presenting with vaginal bleeding in early pregnancy requiring urgent ultrasound.

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Tables and Figures

Table 1: Definitions of Initial Diagnoses	
Initial Diagnosis	Definition
Complete Abortion (CA)*	Loss of products of conception with a previous ultrasound confirming an intrauterine gestational sac or passage of products of conception with or without pathology
Definite Ectopic Pregnancy (DEP)*	Extrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)[12]
Early Pregnancy Failure (EPF)*	Ultrasound findings consistent with criteria set forth for pregnancy failure including crown-rump length ≥7 mm and no heartbeat, mean sac diameter of ≥25 mm with no embryo, absence of embryo with heartbeat ≥2 weeks after a scan that showed a gestational sac without a yolk sac, absence of embryo with heartbeat ≥11 days after a scan that showed a gestational sac with a yolk sac[1]
Incomplete Abortion (IA)*	Vaginal bleeding with or without cramping[19] in addition to presence of retained products of conception on ultrasound
Intrauterine Pregnancy of Uncertain Viability (IUV)	Definitive ultrasonographic evidence of an IUP but milestones are insufficient to state if the gestation is viable[12]
Molar Pregnancy (MP)*	Ultrasonographic evidence of a hydatidiform mole "snowstorm" pattern and/or characteristic histopathologic findings of either a complete or partial hydatidiform mole[13]
Pregnancy of Unknown Location (PUL)	Positive serum hCG value without evidence of either an intra- or extra-uterine pregnancy[1,12]
Probable Ectopic Pregnancy (PE)*	Ultrasound findings of an inhomogenous adnexal mass or extrauterine sac-like structure[12]
Viable Pregnancy (VP)*	Ultrasound demonstrates an intrauterine pregnancy, embryo/fetus has a heartbeat and normal ultrasound milestones for gestational age[12]

*also considered final diagnoses

Table 2: Definitions of Final Diagnoses	
Final Diagnosis	Definition
Ectopic pregnancy – missing pathology (ECT)	Patient with a previous ultrasound demonstrating probable or definite ectopic pregnancy for which surgery was performed, but final pathology is unavailable
Histologic Ectopic Pregnancy (HEP)	Patient with a previous ultrasound demonstrating probable or definite ectopic pregnancy for which surgery was performed and subsequent pathology identifies chorionic villi[12]
Spontaneously Resolved Probable Ectopic Pregnancy (SPE)	Patient with a previous probable ectopic pregnancy managed expectantly to resolution of hCG levels <100 IU/L or sufficient percent decline[11]
Treated Probable Ectopic Pregnancy (TPE)	Patient with a previous probable ectopic pregnancy managed with methotrexate
Histologic Intrauterine Pregnancy (HIUP)	Patient with a previous PUL managed with a uterine evacuation with chorionic villi identified on pathology[12] or patients demonstrating a molar pregnancy on ultrasound, but upon uterine evacuation display no evidence of molar pregnancy on pathology
PUL Appropriately Declining (PULAD)	Patient with a previous PUL managed expectantly showing appropriate percent decline in hCG[11] but not followed below 1000
PUL Inadequate Drop	Patient with a previous PUL managed expectantly demonstrating an

(PULID)	inadequate percent decline in hCG to meet currently available standards[11] but declines to such an extent to be considered a pregnancy loss
Resolved Persistent PUL (PULRP)	Patient with a previous PUL with spontaneous resolution of hCG levels with expectant management or after uterine evacuation without evidence of chorionic villi on pathology[12] or pathology unavailable
Spontaneously Resolved PUL (PULSR)	Patients with a previous PUL with spontaneous resolution of hCG levels[11,12]
Treated Persistent PUL (PULTP)	Medical management [with methotrexate in most cases, one case received vaginal misoprostol and methotrexate] of PUL without confirmation of the location of the gestation[12]
Spontaneous abortion-self resolving (SASR)	A self-resolving intrauterine pregnancy, including cases of early pregnancy failure, incomplete abortion and complete abortion
Spontaneously Resolved Pregnancy (SRP)	Resolving hCG levels as defined for PULSR[11] without an ultrasound diagnosis or medical/surgical intervention

Table 3: Characteristics of groups derived from all EPAC patients seen between 2006-2012

	Initial Ultrasound Diagnosis	Final Diagnosis	Intrauterine Pregnancy of Uncertain Viability*	Pregnancy of Unknown Location*
n	2683	2838	211	727
Viable Pregnancy	1001	1186	83	53
Ectopic Pregnancy	79	155	Excluded	79
DEP	15	2	-	-
ECT	-	5	-	1
HEP	-	39	-	13
PE	54	6	-	2
SPE	-	12	-	2
PULTP	-	38	-	35
TPE	-	53	-	26
IUV	247	-	-	-
PUL	764	-	-	-
Intrauterine Pregnancy Loss	592	1479	128	595
CA	38	318	77	19
EPF	459	416	40	10
HIUP Mean (range)	-	6 (5-7)**	-	5
IA	95	93	11	1
PULAD	-	47	-	47
PULID	-	61	-	60
PULRP	-	9	-	9
PULSR	-	446	-	443
SASR	-	18	-	-
SRP	-	65	-	-
PULTP receiving misoprostol	-	1	-	1
Molar Pregnancy Mean (range)	10	17 (16-18)**	Excluded	Excluded

Mean Age (Range)	29y (14-48y)	28y (14-48y)	29y (17-45y)	28y (15-46y)
Referral				
HSC EDs	92.7%	90.0%	89.6%	92.1%
Obstetricians	2.8%	2.8%	4.7%	3.7%
Other Wpg EDs	1.2%	1.0%	0%	1.5%
Unknown	1.2%	4.3%	0.5%	0.6%
Other	2.1%	1.9%	5.2%	2.1%
Mean Initial hCG (IU/L) (range)	29,851 (5-333,167)	30,452 (5-339,503)	10,484 (168-98,855)	2,459 (5-57,473)
Median Initial hCG (IU/L)	8,589	8,955	6,581	786
Mean time from hCG to initial ultrasound (Range)	24h (-24-72h)	-	19h (-22-71h)	22h (-20-72)
Median time from hCG to initial ultrasound	18h	-	16h	18h
Mean time from hCG to initial EPAC presentation (Range)	-	27h (-13-96h)	-	-
Median time from hCG to initial EPAC presentation	-	19h	-	-
Number of EPAC Visits				
Range	1-14	1-14	1-6	1-14
1 visit (n)	1620	1724	11	286
2 visits (n)	684	725	134	233
≥3 visits (n)	380	389	66	208

*final diagnoses shown
**2 cases of molar pregnancy determined to be HIUP after ROC analyses were performed
EDs: Emergency Departments, see Tables 1 and 2 for abbreviations

Figure 1: Initial hCG ≤136,707 IU/L and the sensitivity, specificity, positive predictive value, and negative predictive value for the final diagnosis of viable pregnancy using final diagnosis group

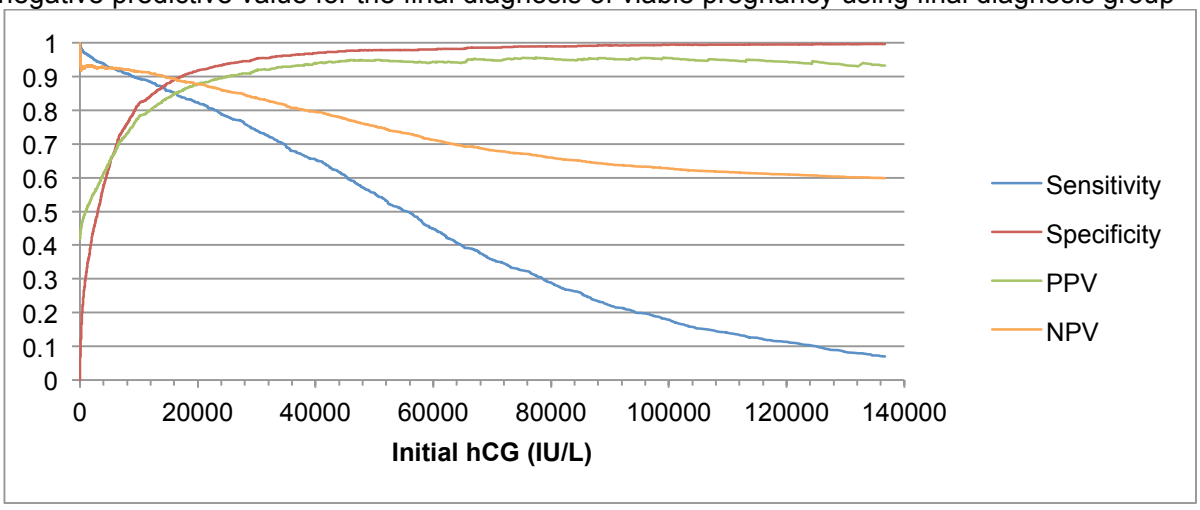


Figure 2: Relationship between initial maximum hCG ≤54,421 IU/L and percentage of initial ultrasound diagnosis of PUL, ectopic pregnancy, viable pregnancy, early pregnancy failure and patients eligible for D&C[1] using initial diagnosis group[2]

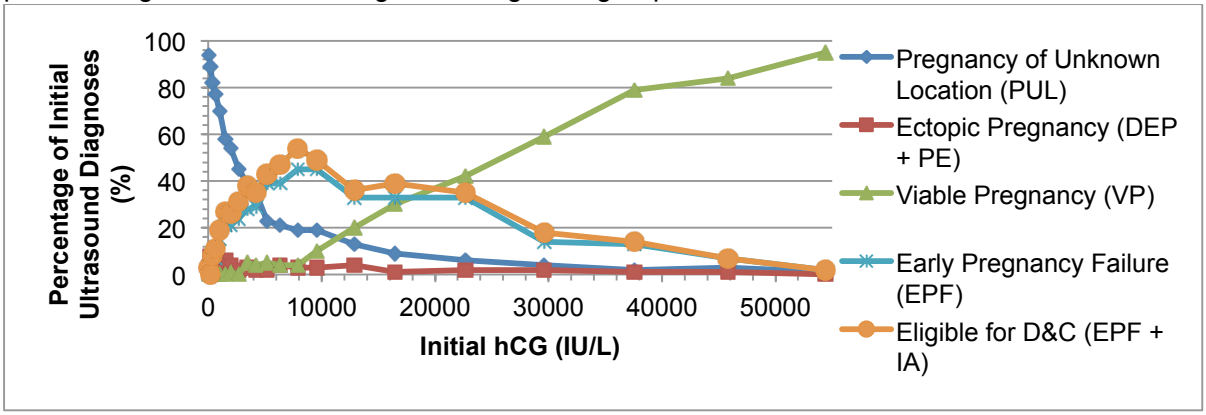


Figure 3: Relationship between initial maximum hCG ≤54,406 IU/L and final diagnosis of ectopic pregnancy, intrauterine pregnancy loss, and viable pregnancy alone using final diagnosis group[3]

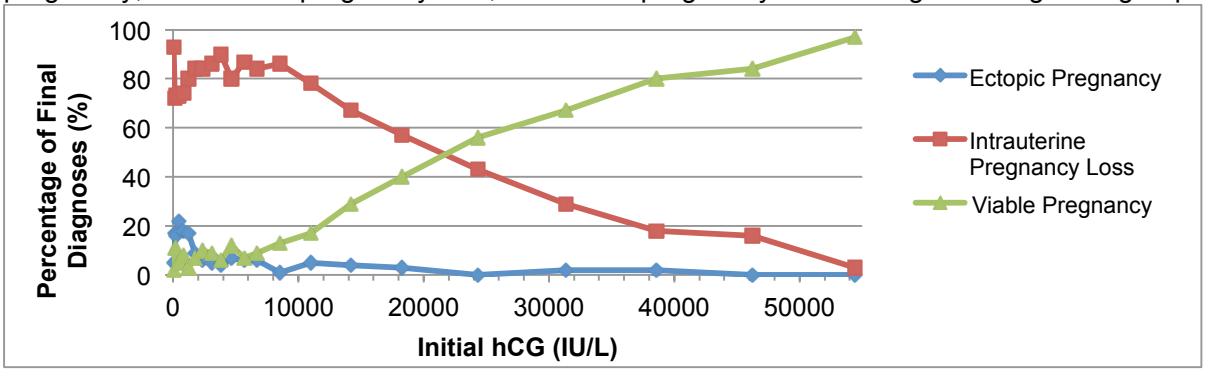
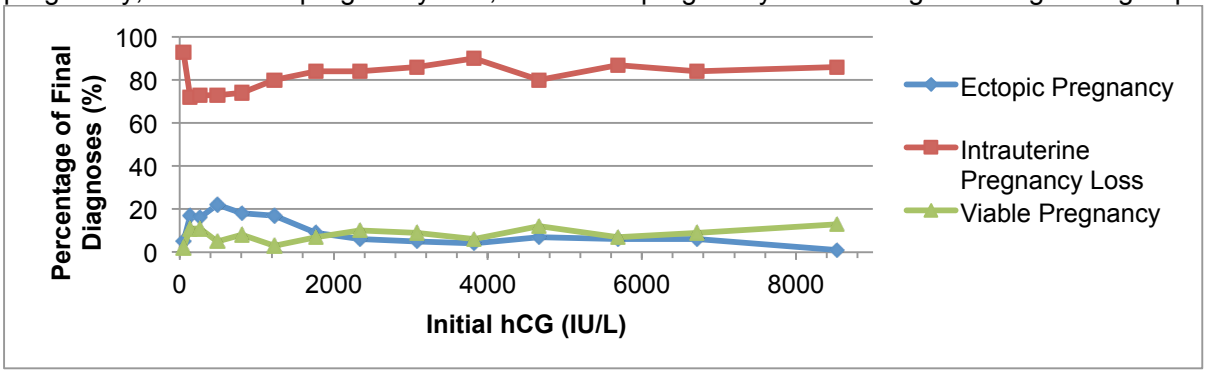


Figure 4: Relationship between initial maximum hCG ≤8,538 IU/L and final diagnosis of ectopic pregnancy, intrauterine pregnancy loss, and viable pregnancy alone using final diagnosis group[3]



[1] D&C: dilation and curettage
[2] Initial diagnosis group ordered by ascending hCG and displayed in categories of 100 patients, each plotted hCG value represents a range, for which only the maximum hCG is shown
[3] Final diagnosis group ordered by ascending hCG and displayed in categories of 100 patients, each plotted hCG value represents a range, for which only the maximum hCG is shown